Sven Graßmann[a], Joachim Apelt[a], Xavier Ligneau[b], Heinz H. Pertz[a], Jean-Michel Arrang[c], C. Robin Ganellin[d], Jean-Charles Schwartz[b,c], Walter Schunack[a], Holger Stark[e]

[a] Institut für Pharmazie, Freie Universität Berlin, Berlin, Germany
[b] Laboratoire Bioprojet, Paris, France
[c] Unité de Neurobiologie et Pharmacologie Moléculaire (U. 573),Centre Paul Broca de l'INSERM, Paris, France
[d] Department of Chemistry, Christopher Ingold Laboratories, University College London, London, UK
[e] Johann Wolfgang Goethe-Universität, Biozentrum, Institut für Pharmazeutische Chemie, ZAFES, Frankfurt am Main, Germany

Search for Histamine H_3 Receptor Ligands with Combined Inhibitory Potency at Histamine *N*-Methyltransferase: ω-Piperidinoalkanamine Derivatives

In an effort to design new hybrid compounds with dual properties, i.e. binding affinity at histamine H_3 receptors and inhibitory potency at the catabolic enzyme histamine N^{τ}-methyltransferase (HMT), a novel series of 1-substituted piperidine derivatives was synthesized. This alicyclic heterocycle is structurally linked via aminoalkyl spacers of variable lengths to additional aromatic carbo- or heterocycles. These new hybrid drugs were pharmacologically evaluated regarding their binding affinities at recombinant human H_3 receptors, stably expressed in CHO cells, and in a functional assay for their inhibitory potencies at rat kidney HMT. All compounds investigated proved to be H_3 receptor ligands with binding affinities in the micro- to nanomolar concentration range despite significant differences in the type of the aromatic moiety introduced. The most potent compound in this series was the quinoline derivative **20** (K_i = 5.6 nM). Likewise, all new ligands studied showed impressive HMT inhibitory activities. Here, compounds **5**, **10**, **14,** and **18**−**20** exhibited submicromolar potencies (IC_{50} = 0.061−0.56 μM). The aminomethylated quinoline **19** showed almost the same, well balanced nanomolar activities on both targets. In this study, new hybrid compounds with a dual mode biological action were developed. These pharmacological agents are valuable leads for further development and candidates for treatment of histamine-dependent disorders.

Keywords: Histamine *N*-methyltransferase; Histamine H_3 receptor; Inhibitor; Ligand; Antagonist

Received: April 20, 2004; Accepted: August 11, 2004 [FP897]
DOI 10.1002/ardp.200400897

Full Paper

Introduction

The histamine receptor family consists of four different members, H_1−H_4 [1, 2]. Although G protein-coupled histamine H_3 receptors were described two decades ago by an elegant set of pharmacological experiments [3], their cloning and molecular characterization was not achieved until recently [4]. Today, valuable H_3 receptor information is available from various species, such as rat [5], mouse [6], guinea-pig [7], monkey [8], and human [4]. Major progress was also achieved to understand expression patterns, receptor subtypes, species-related pharmacological diversity [9], and constitutive activity [10]. Predominantly, brain localized [11] H_3 receptors are found in (non-)histaminergic neurons [3] and activation leads to inhibition of adenylyl cyclases via G_i proteins [4]. Synthesis and release of numerous neurotransmitters such as histamine [12], noradrenaline, serotonin, acetylcholine, and glutamate as well as several peptides, e.g. substance P [1], are modulated upon their stimulation.

Since H_3 autoreceptors are localized presynaptically and display high constitutive activity [10], inverse agonists enhance histamine release by decreasing the negative feedback mechanism. Because of the receptors' influence on numerous signal transduction mechanisms and important (patho)physiological processes, e.g. arousal and mood control [13], antagonists/inverse agonists of histamine H_3 receptors are of special therapeutic interest. A huge number of potent antagonists of numerous chemical and pharmacological classes with different properties have been described [14−18]. Apart from their potential application as cognition enhancers, e.g. in Alzheimer's disease [19, 20] or memory and learning deficits [21], an H_3 receptor ligand has entered a phase II clinicial study for attention-deficit hyperactivity disorder [17, 22].

Correspondence: Holger Stark, Johann Wolfgang Goethe-Universität, Biozentrum, Institut für Pharmazeutische Chemie, ZAFES, Marie-Curie-Strasse 9, D-60439 Frankfurt am Main, Germany. Phone: +49 69 798-29302, Fax: +49 69 798-29258, e-mail: h.stark@pharmchem.uni-frankfurt.de

Histamine is biosynthesized by decarboxylation of the precursor L-histidine through cytoplasmatic L-histidine decarboxylase (E.C. 4.1.1.22), stored in vesicles, and released from axon terminals in a rapid-turnover mechanism to function as a neurotransmitter [13, 23]. Histamine undergoes inactivation catalyzed either by the non-specific enzyme diamine oxidase (DAO, E.C. 1.4.3.6) [24] or by the ubiquitously distributed enzyme histamine *N*-methyltransferase (HMT, E.C. 2.1.1.8) [25]. Since oxidative deaminating DAO is not found in the CNS to inactivate histamine [26], methylation in the N^{τ}-position of the imidazole ring of histamine by HMT with *S*-adenosyl-L-methionine as methyl donor is the only possibility in CNS neurons [27]. Further down the pathway in the brain, the metabolite N^{τ}-methylhistamine is converted by MAO-B (E.C. 1.4.3.4) and, subsequently, into (N^{τ}-methylimidazol-4-yl)acetic acid [23, 24] by special oxidases. Since the key metabolite N^{τ}-methylhistamine, like all other metabolites, is inactive at the different members of the histamine receptor family [11], HMT represents the decisive enzyme for the inactivation of histamine in the CNS [28]. Therefore, measurement of the N^{τ}-methylhistamine level to determine H_3 receptor-dependent brain activation or inactivation *in vivo* is a well established pharmacological method [10]. Whereas potent H_3 receptor antagonists/inverse agonists increase histamine release, potent HMT inhibitors are described to selectively increase histamine concentrations in the brain being highly specific for their substrate histamine [29]. In two recent systematic structure-activity surveys [30, 31] in this new field of selective regulation of histaminergic neurotransmission, our research group has described two structurally different series of hybrid compounds which combine both, H_3 receptor antagonist properties and HMT inhibitory activities, in a single molecule. The first series consists of highly potent non-imidazole compounds, the most interesting member among these is probably the piperidine derivative FUB 854 (Figure 1), a potent non-imidazole histamine H_3 receptor antagonist (K_i = 19 nM) and highly active HMT inhibitor (IC_{50} = 34 nM) [30]. In a first attempt to extend this dual mode of synergistic action to other structural classes, the second series contains a number of potent imidazole derivatives, e.g. FUB 818 (Figure 1), a hybrid compound with high potency at H_3 receptors (K_i = 4.1 nM), as well as high inhibitory HMT activity (IC_{50} = 24 nM) [31].

In this study, we have expanded our work into the field of non-imidazole compounds with combined pharmacological action, medium to high affinity for the human H_3 receptor and HMT inhibitory potency. We describe a novel series of hybrid compounds with various chemical structures which, as integral parts of their molecules, possess structures partially derived from the described prototypic HMT inhibitors FUB 854 and FUB 818, the antidementia drug tacrine [20], or the antimalarial agent metoprine, the latter two also exhibit significant HMT inhibitory activity (Figure 1) [32]. The partial structures derived from corresponding aminoheterocycles, probably causing HMT inhibition, were linked, via alkyl spacers of variable lengths, to a piperidine ring, presumably affecting H_3 receptor binding. Generally, new hybrid compounds are not only valuable because of their single pharmacokinetics and toxicology as opposed to the combined application of an H_3 receptor antagonist and an HMT inhibitor, they might also become useful in the treatment of psychiatric and neurodegenerative diseases and for pharmacological investigations.

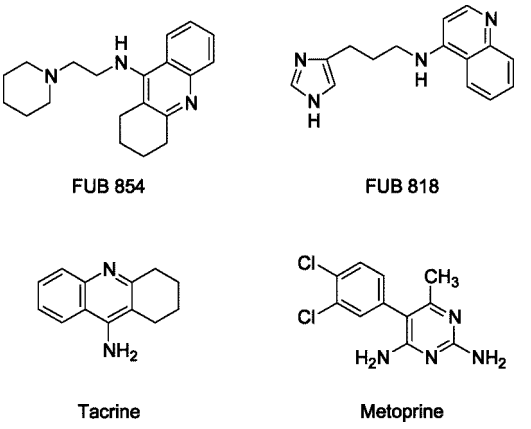


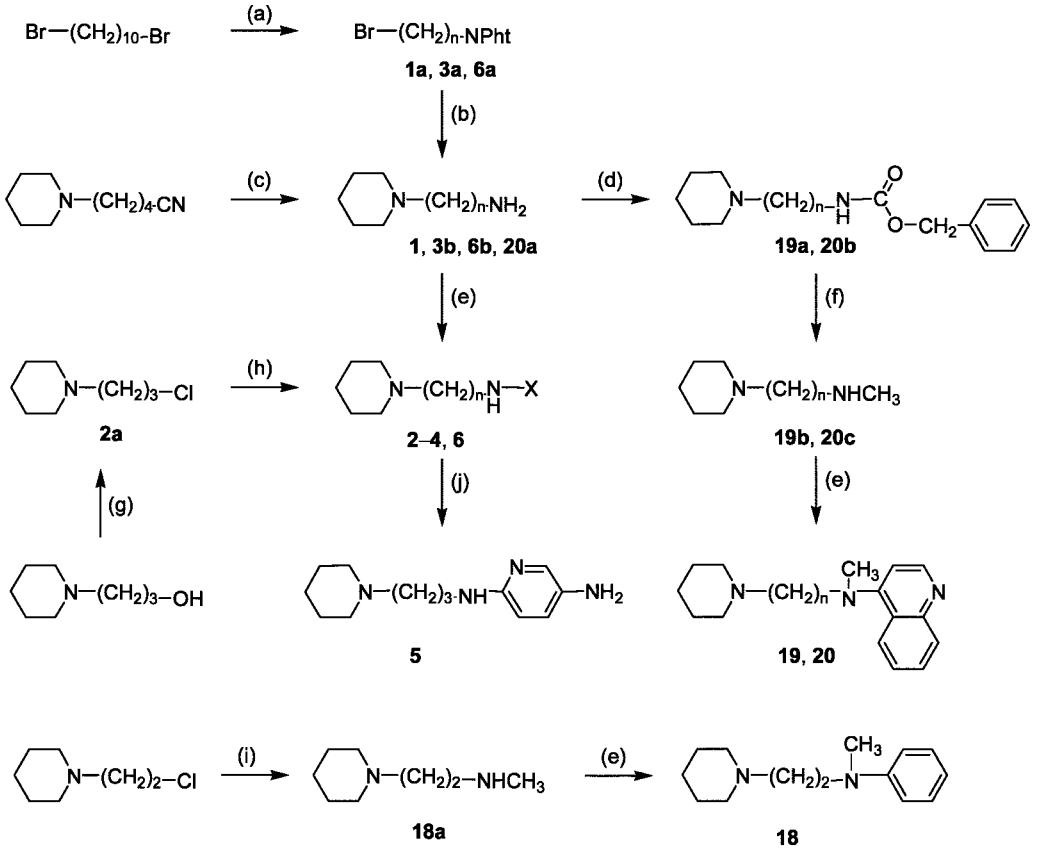
Figure 1. FUB 854 and FUB 818, prototypic HMT inhibitors with combined histamine H_3 receptor antagonist potency; tacrine and metoprine, inhibitors of HMT.

The compounds described herein were investigated in two different pharmacological test systems. Binding affinities at human H_3 receptors stably expressed in CHO cells *in vitro* and inhibitory activities at rat kidney HMT were determined.

Results and discussion

Chemistry

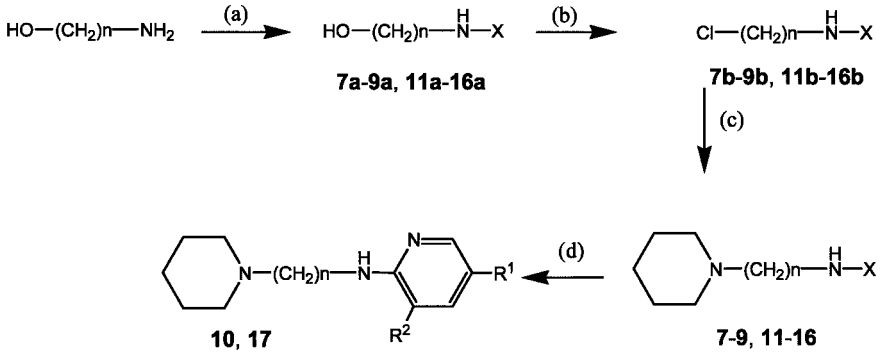
The novel amine derivatives **1**–**6** were synthesized via different pathways as outlined in Scheme 1. 10-Aminodecylpiperidine (**1**) was obtained in two steps from commercially available 1,10-dibromodecane by converting one bromo substituent into the corresponding phthalimide functionality (**1a**) followed by alkylation



† n, 10 (**1**, **1a**), 3 (**2**–**5**, **3a**, **3b**), 4 (**6**, **6a**, **19**, **19a**, **19b**), 5 (**20**, **20a**, **20b**); X, 1-naphthyl (**2**), (4,6-dimethoxy)-1,3,5-triazin-2-yl (**3**), (5-nitro)pyridine-2-yl (**4**, **6**); quinolin-4-yl (**19**, **20**); (a) KNPht, KI, acetone, 3 d, 50 °C; (b) *i.* piperidine, KI, acetone, 12 h, 50 °C; *ii.* 6 N HCl, 12 h, reflux; (c) H_2 (10 bar), Raney nickel, 25 % NH_3, 20 h, r.t.; (d) chloroformic acid benzyl ester, 2 N NaOH, THF, 2 h, r.t.; (e) Cl–X, phenol, KI, 1 h, 140 °C (**3**, **18**–**20**); Cl–X, $N(C_2H_5)_3$, KI, EtOH, 12 h, reflux (**4**, **6**); (f) $LiAlH_4$, THF, 3 h, reflux; (g) $SOCl_2$, THF, 2 h, 50 °C; (h) 1-naphthylamine, NaH, *N*,*N*-dimethylformamide, 12 h, 140 °C; (i) H_2NCH_3, KOH, KI, MeOH, H_2O, 12 h, reflux; (j) H_2 (1 bar), Pd/C, THF, 12 h, r.t. (similar procedure for **8** → **10**, **15** → **17**).

Scheme 1. Synthesis of amine derivatives **1**–**6** and **18**–**20**†.

with piperidine and subsequent acidic cleavage of the protecting group. Regarding the compounds containing a three-carbon spacer, the naphthyl derivative **2** was synthesized by alkylation of 1-naphthylamine under basic conditions with intermediate **2a**, which was obtained by conversion of the corresponding alcohol to the alkyl chloride. Other compounds of this type, the final compounds **3**, **4**, and **6**, were prepared from the corresponding *N*-(ω-bromoalkyl)phthalimides by reaction with piperidine and then hydrochloric acid as described in the synthesis of **1**, followed by amination of the appropriate aryl chlorides. To improve the yields of compound **3**, the latter reaction was carried out in molten phenol in which the formation of unstable phenol ether intermediates with the heterocycles causes increased reactivities as leaving groups compared to those of aryl halides [33]. In contrast, **3b** and **6b** (precursors of **4** and **6**, respectively) were reacted in ethanol. The derivative containing a primary aromatic amine function at the pyridine moiety (**5**) was obtained



† n, 5 (**7a–9a, 7b–9b, 7–10**), 6 (**11a–14a, 16a, 17a, 11b–14b, 16b, 17b, 11–17**); X, (3-nitro)pyridine-2-yl (**7, 15**), (5-nitro)pyridin-2-yl (**8, 16**), (3,5-dinitro)pyridine-2-yl (**9**), benzo[d][1,3]thiazol-2-yl (**11**), quinolin-2-yl (**12**), pyrimidin-2-yl (**13**), pyridin-4-yl (**14**); R^1 = H, R^2 = NH_2 (**8** → **10**), R^1 = NH_2, R_2 = H (**15** → **17**); (a) Cl–X, $N(C_2H_5)_3$, KI, EtOH, 12 h, reflux (**7–9, 12, 16**); Cl–X, phenol, KI, 12 h, 140 °C (**11, 13–15**); (b) $SOCl_2$, THF, 2 h, 50 °C; (c) piperidine, K_2CO_3, KI, EtOH, 12 h, reflux; (d) H_2 (1 bar), Pd/C, THF, 12 h, r.t.

Scheme 2. Synthesis of amine derivatives **7**−**17**†.

by reduction of the nitro group of **4** under hydrogen and palladium catalysis.

In contrast to the derivatives outlined above, amine derivatives **7**−**17** possess five or six methylene groups in the spacer link between the piperidine moiety and the secondary amine. All compounds, except for **10** and **17** (obtained by an additional final reduction step), were synthesized straightforwardly in three steps starting from commercially available ω-aminoalkanols by reaction with the corresponding aryl halides resulting in the *N*-substituted intermediates (Scheme 2). As described before, this step was carried out either in ethanol (**7**−**9**, **12**, **16**) or, more conveniently, in molten phenol (**3**, **11**, **13**−**15**, **18**−**20**). Subsequently, the intermediate alcohols were converted into the alkyl chlorides followed by reaction with piperidine under basic conditions. The final compounds **8** and **15** were further reacted with hydrogen and catalytic amounts of palladium on charcoal to convert the nitro groups into primary amino groups resulting in pyridine derivatives **10** and **17**.

The precursor of compound **18** (**18a**) was obtained from **2a** by alkylation of methanamine. Then, it was reacted in molten phenol with 4-chloropyridine to give **18** in good yield. The quinoline derivatives **19** and **20** were synthesized in a different procedure: 4-piperidinobutan- (**6b**) or 5-piperidinopentanamine (**20a**) were acylated to carbamates and then reduced to yield precursors **19b** and **20c**. The aforementioned primary amine derivative **20a** was obtained from the corresponding nitrile by reduction with hydrogen and Raney nickel. In the final step, **19b** and **20c** were alkylated with phenol as solvent by the procedure described before.

Pharmacology and discussion

Binding affinity at human histamine H_3 receptors

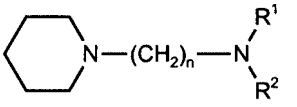
The new compounds were pharmacologically investigated for their binding affinity at cloned human histamine H_3 receptors in stably expressed CHO cells by a [^{125}I]iodoproxyfan binding assay [30]. The results of the pharmacological screening are summarized in Table 1. It is obvious that all compounds investigated, with the exception of **4** (K_i = 1186 nM), clearly displayed binding affinity for H_3 receptors with affinities from the low to high nanomolar concentration range (K_i = 5.6−484 nM). Compound **1**, the only primary amine of this series of *N*-substituted piperidine derivatives with ten methylene groups between piperidine and the amino moiety, showed remarkable affinity for H_3 receptors. In contrast to **1**, all other compounds in this series possess a (hetero)aromatic moiety with an exocyclic nitrogen linked by a spacer of 2 to 6 methylene groups to a piperidino group. While the 5-nitropyridine derivative **4** displays only affinity in the micromolar concentration range, its reduced equivalent **5**

binds with nanomolar potency. The comparable differences are less pronounced with compounds **8**–**10** and **15**–**17**. Major progress was obtained with compounds **12**–**17**, all having a six-membered alkyl spacer in common. The nature of the heteroaromatic moiety attached at the exocyclic nitrogen seems to be of minor importance, as all compounds show remarkable affinities with K_i values below 100 nM. Compound **13** was evaluated for its ability to effect the release of [^{3}H]histamine on synaptosomes of rat cerebral cortex and showed, as expected, impressive antagonist activity in this functional assay for *in vitro* determination of histamine H_3 receptor potency [34]. Compounds **18**–**20** have the tertiary amino functionality at the heteroaromatic moiety in common. As observed before, a longer alkyl chain in the spacer seems to be beneficial. The quinoline derivative **20** was the most potent H_3 receptor ligand described in this study.

In vitro screening for HMT inhibitory activity

The new compounds were investigated for inhibition of rat kidney HMT activity based on the quantitative determination of the metabolite N^{τ}-methylhistamine. All compounds investigated inhibit rat kidney HMT (Table 1). The pharmacological data of the new ω-piperidinoalkanamine derivatives are comparable to that of the reference HMT inhibitor tacrine [30]. Here, depending on the type of the aromatic substituent introduced, major differences in inhibitory potencies could be detected. In general, the inhibitory activities were

Table 1. Chemical structures and results of pharmacological screening of ω-piperidinoalkanamine derivatives for human histamine H_3 receptor binding affinity and inhibitory potency at rat histamine *N*-methyltransferase.



No.	n	R^1	R^2	H_3 K_i (nM)†	HMT-Inhibition IC_{50} ± SEM (μM)‡
1	10	H	H	46	21 ± 2
2	3	H	naphth-1-yl	135	1.8 ± 0.1
3	3	H	(4,6-dimethoxy)-1,3,5-triazin-2-yl	n.d.#	62 ± 1
4	3	H	(5-nitro)pyridin-2-yl	1186	8.0 ± 1.6
5	3	H	(5-amino)pyridin-2-yl	59	0.35 ± 0.08
6	4	H	(5-nitro)pyridin-2-yl	471	5.1 ± 0.5
7	5	H	(3-nitro)pyridin-2-yl	484	29 ± 2
8	5	H	(5-nitro)pyridin-2-yl	210	6.0 ± 0.9
9	5	H	(3,5-dinitro)pyridin-2-yl	181	6.4 ± 1.5
10	5	H	(5-amino)pyridin-2-yl	125	0.17 ± 0.07
11	6	H	benzo[d][1,3]thiazol-2-yl	119	6.2 ± 0.5
12	6	H	quinolin-2-yl	26	1.1 ± 0.1
13	6	H	pyrimidin-2-yl	95§	59 ± 6
14	6	H	pyridin-4-yl	36	0.56 ± 0.09
15	6	H	(3-nitro)pyridine-2-yl	66	22 ± 2
16	6	H	(5-nitro)pyridin-2-yl	90	3.6 ± 0.7
17	6	H	(3-amino)pyridin-2-yl	55	6.1 ± 0.8
18	2	CH_3	pyridin-4-yl	210	0.23 ± 0.3
19	4	CH_3	quinolin-4-yl	67	0.061 ± 0.001
20	5	CH_3	quinolin-4-yl	5.6	0.075 ± 0.005
Tacrine††				n.d.	0.11 ± 0.04

† [^{125}I]Iodoproxyfan binding assay at human H_3 receptors stably expressed in CHO cells [40]; ‡ HMT assay on isolated enzyme from rat kidney (mean value with standard error of the mean (SEM)) [30]; # n.d., not determined; § functional H_3 receptor *in vitro* assay on synaptosomes of rat cerebral cortex [34]; †† data from reference [30].

in the moderate micromolar to submicromolar concentration range (IC_{50} = 0.17−62 μM). The compounds, having integrated either a 4-substituted pyridine (**14**, **18**) or a 2-substituted 5-aminopyridine moiety (**5**, **10**), display high inhibitory potencies. Comparing the 3-nitropyridine derivative **15** to its corresponding 3-aminopyridine equivalent **17**, inhibitory potency could be enhanced more than threefold. Likewise but more pronounced, comparison of the respective 5-nitropyridine derivatives with their 5-aminopyridine analogues (**4** vs. **5**, **8** vs. **10**) showed a more than twenty-fold increase of the inhibitory activity in both examples. The most potent HMT inhibitors in this series were the aminopyridine derivatives **5**, **10**, **14**, and **18** with inhibitory potencies comparable to that of the prototype tacrine [35] and, especially, the aminomethylated quinoline derivatives **19** and **20,** having a higher potency than tacrine. It seems that methylation of the amino functionality and the larger heteroaromatic moiety lead to increased HMT affinity.

Conclusion

In this study, we report on novel potent histamine H_3 receptor ligands with combined HMT inhibitory activities. These new compounds are 1-substituted piperidines and, except for **1** (primary amine) and **2** (naphthyl derivative), consist, in addition, of structurally and electronically different amino(hetero)aromatic moieties. These two diverse parts of the molecules are linked via an alkyl spacer to cause the dual mode of the biological action. The structural elements used are described in our previous work and in other related publications.

In vitro investigation of the new compounds in two different test systems proved their H_3 receptor binding affinities as well as the inhibitory potencies at the histamine metabolizing enzyme. The new compounds presented here differ in their biological potencies depending on the type of heterocycle which is presumably responsible for the inhibition of HMT.

The concept of joining both modes of action in one molecule was successful. Several of the new hybrid molecules show remarkable affinity for human H_3 receptors. Although the compounds tested are quite different in the nature of their heterocycle and in the substitution pattern, the H_3 receptor affinities remain more or less in the moderate or high nanomolar concentration range, with the exception of **4** and **20** in different directions. In the course of this study, the derivatives, particularly possessing 4-substituted pyridine moieties (**14**, **18**) and two compounds containing 2-substituted 5-aminopyridine moieties (**5**, **10**), were identified as potent histamine HMT inhibitors. These results suggest that compounds with a designated optimal balance between H_3 receptor potency and HMT inhibitory activity could be designed as needed. In this respect, compound **19** is active on both targets in a comparable nanomolar concentration range whereas **20** with rather similar HMT inhibitory potency is even 10 times more potent at human H_3 receptors than **19**. In addition, the combined properties in one molecule may have potential benefits regarding sole pharmacokinetics and toxicology or at least differences in metabolism. This makes the hybrid approach with ω-piperidinoalkanamine derivatives not only interesting regarding the development of lead compounds for further optimization but it also produces potentially interesting candidates for further improvement in the development of therapeutics for histamine-related CNS disorders.

Acknowledgments

This work was supported by the Biomedical Health Research Program (BIOMED) of the European Union and the Fonds der Chemischen Industrie, Verband der Chemischen Industrie, Frankfurt/Main, Germany.

Experimental

Chemistry

General procedures

Melting points (mp) were determined on an Electrothermal IA 9000 digital (Electrothermal, Essex, UK) or a Büchi 512 apparatus (Büchi Labortechnik, Flawil, Switzerland) and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker DPX 400 Avance spectrometer (400 MHz, Bruker, Rheinstetten, Germany) in dimethyl sulfoxide-d_6 as standard solvent, unless stated otherwise. Chemical shifts are reported in ppm downfield from internal tetramethylsilane as a reference. ^{1}H NMR signals are reported in order: multiplicity (s, singlet; d, doublet; dd, doublet of a doublet; t, triplet; m, multiplet; *, exchangeable by H_2O-d_2), approximate coupling constants (J), and number of protons. EI mass spectra were obtained on a Finnigan MAT CH7A (70 eV, 170 °C) and FAB$^+$ spectra were recorded on a Finnigan MAT CH5DF (Xe, 80 eV, dimethyl sulfoxide as solvent, glycerol as matrix) (Thermo Electron Corporation, Bremen, Germany). Elemental analyses (C, H, N) were measured for final compounds on Perkin-Elmer 240 B or Perkin-Elmer 240 C instruments (Perkin-Elmer, Beaconsfield, U.K.) and are within ±0.4 % of the theoretical values. The compounds were crystallized and recrystallized at least once either directly or as salts of oxalic acid or hydrochloric acid from EtOH/Et_2O, unless indicated otherwise. Elemental analysis for compounds with unexpected stoichiometric salt formations was only stated when two separate crystallizations gave the same result and, simultaneously, other analysis techniques showed no traces of impurities. Column chromatography was carried out using silica gel 63−200 μm (Merck, Darmstadt, Germany). Flash chromatography was performed with silica gel 40−63 μm

(Merck). Preparative, centrifugally accelerated, rotatory chromatography (eluent: $CHCl_3$, NH_3 atmosphere) was performed using a Chromatotron 7924T (Harrison Research, Palo Alto, CA, USA) and glass rotors with 4 mm layers of silica gel 60 F_{254} containing gypsum (Merck). Thin layer chromatography was performed on silica gel F_{254} plates (Merck). The following abbreviations are used: ax, axial; b.p., boiling point; Benz, benzo[d][1,3]thiazolyl; br, broad; eq, equatorial; CF_3COOD, trifluoroacetic acid-d_1; EtOAc, ethyl acetate; EtOH, ethanol; m.p., melting point; KNPht, potassium phthalimide; MeOH, methanol; Naph, naphthyl; Ph, phenyl; Pht, phthalimido; Pip, piperidinyl; Py, pyridyl; Pyr, pyrimidinyl; Quin, quinolinyl; r.t., room temperature; sat., saturated; THF, tetrahydrofuran.

*N-(10-Bromodecyl)phthalimide (**1a**)*

1,10-Dibromodecane (15 g, 50 mmol) and a catalytic amount of KI in acetone (30 mL) were stirred at 50 °C. After addition of KNPht (4.6 g, 25 mmol) in small portions and subsequent stirring for 3 d at 50 °C, the suspension was filtered. After removal of the solvent *in vacuo* the crude product was purified by flash chromatography (eluent: petroleum ether → petroleum ether/MeOH; 2:3). Yield: 72%; $C_{18}H_{24}BrNO_2$ (366.3) [36]; m.p. 62–63 °C; ^{1}H-NMR δ 7.82–7.88 (m, 4H, Pht-H), 3.56 (t, *J* = 7.1 Hz, 2H, CH_2Pht), 3.50 (t, *J* = 6.7 Hz, 2H, $BrCH_2$), 1.77 (m, 2H, $BrCH_2CH_2$), 1.58 (m, 2H, CH_2CH_2Pht), 1.24–1.37 (m, 12H, $BrCH_2CH_2(CH_2)_6$); EI-MS *m/z* (%) 366 ($M^{+\bullet}$, 7).

*General procedure for the preparation of compounds **1**, **3b**, **6b***

The corresponding *N*-(ω-bromoalkyl)phthalimide (10 mmol) and piperidine (30 mmol) were dissolved in acetone (20 mL) and stirred for 12 h at 50 °C. The suspension was filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography (eluent: CH_2Cl_2/NH_3-sat. MeOH; 95:5). After refluxing with aqueous HCl (*c* = 6 mol/L, 50 mL) for 12 h the solvent was removed *in vacuo*.

*10-Piperidinodecanamine dihydrogen oxalate (**1**)*

From **1a** (15 g, 50 mmol), eluent: CH_2Cl_2/MeOH/$N(C_2H_5)_3$ 90:5:5. Aqueous HCl (*c* = 2 mol/L) was used. Subsequently, the solution was washed with EtOAc, basified and extracted with CH_2Cl_2. Yield: 54%; $C_{15}H_{32}N_2{\cdot}2C_2H_2O_4{\cdot}0.75H_2O$ (434.0); m.p. 116.1–117.2 °C; ^{1}H-NMR δ 3.04 (m, 4H, Pip-2,6H), 2.90 (t, *J* = 8.1 Hz, 2H, PipCH_2), 2.75 (t, *J* = 7.5 Hz, 2H, CH_2NH_2),1.50–1.72 (m, 10H, Pip-3,4,5H, $PipCH_2CH_2$, C$H_2CH_2NH_2$), 1.27 (m, 12H, $PipCH_2CH_2(CH_2)_6$); EI-MS *m/z* (%) 240 ($M^{+\bullet}$, 9); C, H, N.

*3-Piperidinopropanamine dihydrochloride (**3b**)*

From commercially available *N*-(3-bromopropyl)phthalimide (**3a**, 2.68 g, 10 mmol). Yield: 60%; $C_8H_{18}N_2{\cdot}2HCl$ (215.2) [36]; b.p. (base) 101 °C (33 mbar); ^{1}H-NMR δ 8.22* (s, 1H, NH), 3.34–3.38 (m, 4H, Pip-2,5H_{eq}, CH_2NH_2), 2.81–2.88 (m, 4H, Pip-2,6H_{ax}, $PipCH_2$), 2.05 (m, 2H, $PipCH_2CH_2$), 1.67–1.85 (m, 5H, Pip-3,5H, Pip-4H_{eq}), 1.40 (m, 1H, Pip-4H_{ax}); EI-MS *m/z* (%) 142 ($M^{+\bullet}$, 7).

*4-Piperidinobutanamine (**6b**)*

From commercially available *N*-(4-bromobutyl)phthalimide (**6a**, 5.64 g, 20 mmol), eluent: CH_2Cl_2/NH_3-sat. MeOH; 8:2. Yield: 85%; $C_9H_{20}N_2$ (156.3) []; b.p. 103–105 °C (16 mbar); ^{1}H-NMR δ 8.05* (s, 1H, NH), 3.31 (m, 4H, Pip-2,6H_{eq}, CH_2NH_2), 2.93 (m, 2H, Pip-2,6H_{ax}), 2.79 (t, *J* = 7.4 Hz, 2H, $PipCH_2$), 1.55–1.76 (m, 10H, Pip-3,4,5H, $PipCH_2(CH_2)_2$); EI-MS *m/z* (%) 156 ($M^{+\bullet}$, 6).

*1-(3-Chloropropyl)piperidine hydrochloride (**2a**)*

To a solution of 3-piperidinopropanol (0.43 g, 3 mmol), prepared according to Meier et al. [40], in dry THF (20 mL), $SOCl_2$ (0.59 g, 5 mmol) was added under ice-cooling. After stirring for 2 h at 50 °C excess $SOCl_2$ was removed under reduced pressure. Yield: 97%; $C_8H_{16}ClN{\cdot}HCl$ (198.1); ^{1}H-NMR δ 10.53* (s, 1H, NH^+), 3.73 (t, *J* = 6.4 Hz, 2H, CH_2Cl), 3.38–3.41 (m, 2H, Pip-2,6H_{eq}), 3.06–3.10 (m, 2H, PipCH_2), 2.80–2.89 (m, 2H, Pip-2,6H_{ax}), 2.19 (m, 2H, CH_2CH_2Cl), 2.16–2.23 (m, 5H, Pip-3,5H, Pip-4H_{eq}), 1.75–1.81 (m, 1H, Pip-4H_{ax}); EI-MS *m/z* (%) 161 ($M^{+\bullet}$, 3).

*N-(3-Piperidinopropyl)-1-naphthylamine hydrogen oxalate (**2**)*

1-Naphthylamine (0.71 g, 5 mmol) in dry THF (20 mL) and NaH (suspended in mineral oil, ω = 60%, 0.3 g, 7.5 mmol) were stirred at 60 °C for 1 h. After cooling to r.t. and addition of **2a** (base, 0.4 g, 2.5 mmol) and catalytic amounts of tetrabutylammonium chloride, the mixture was refluxed for 12 h. After removal of the solvent under reduced pressure and addition of EtOAc/H_2O, the organic layer was washed several times with a sat. aqueous solution of K_2CO_3 and then extracted with aqueous HCl (*c* = 2 mol/L). After washing with EtOAc, the aqueous layer was basified and extracted with CH_2Cl_2. The solvent was removed under reduced pressure. Yield: 45%; $C_{18}H_{24}N_2{\cdot}C_2H_2O_4$ (358.4); m.p. 219.4–219.9 °C; ^{1}H-NMR (CF_3COOD) δ 8.14 (d, *J* = 8.3Hz, 1H, Naph-8H), 8.10 (d, *J* = 8.0 Hz, 1H, Naph-4H), 7.98 (d, *J* = 8.3 Hz, 1H, Naph-5H), 7.72–7.82 (m, 3H, Naph-2,6,7H), 7.62 (dd, $J_{2H/3H}$ = 7.7 Hz, $J_{3H/4H}$ = 8.1 Hz, 1H, Naph-3H), 7.28 (br, 1H, NH), 3.97 (t, *J* = 7.9 Hz, 2H, CH_2NHNaph), 3.77 (m, 2H, Pip-2,6H_{eq}), 3.37 (m, 2H, $PipCH_2$), 3.03 (m, 2H, Pip-2,6H_{ax}), 2.60 (m, 2H, $PipCH_2CH_2$), 1.84–2.09 (m, 5H, 2Pip-3,5H, Pip-4H_{eq}), 1.60 (m, 1H, Pip-4H_{ax}); EI-MS *m/z* (%) 268 ($M^{+\bullet}$, 10); C, H, N.

*N-Methyl-2-piperidinoethanamine (**18a**)*

$H_2NCH_3{\cdot}HCl$ (2.03 g, 30 mmol), KOH (2.8 g, 50 mmol), commercially available 1-(2-chloroethyl)piperidine·HCl (0.5 g, 7.5 mmol) and catalytic amounts of KI in H_2O (30 mL) were refluxed for 12 h. The mixture was extracted with CH_2Cl_2 and purified by flash chromatography (eluent: CH_2Cl_2/NH_3-sat. MeOH; 95:5). Yield: 25%; $C_8H_{18}N_2$ (142.2) [39]; b.p. 54–58 °C (13 mbar); ^{1}H-NMR (CF_3COOD) δ 3.77–3.91 (m, 4H, CH_2NHCH_3, Pip-2,6H_{eq}), 3.09–3.23 (m, 7H, $PipCH_2$, Pip-2,6H_{ax}, NHCH_3), 2.03–2.10 (m, 5H, Pip-3,5H, Pip-4H_{eq}), 1.64 (m, 1H, Pip-4H_{ax}); EI-MS *m/z* (%) 142 ($M^{+\bullet}$, 2).

*General procedure for the preparation of compounds **3**, **18–20***

The corresponding amine (2.5 mmol) and the corresponding aryl halogenide (2.5 mmol) were heated together with phenol (3 g, 31.9 mmol) for 12 h at 140 °C. After cooling, aqueous NaOH (*c* = 6 mol/L) and EtOAc were added and the mixture was stirred 1 h at r.t. The organic layer was extracted thoroughly with aqueous NaOH (*c* = 6 mol/L). The organic layer was concentrated *in vacuo* and the crude product purified by rotatory chromatography.

*N-(3-Piperidinopropyl)-4,6-dimethoxy-1,3,5-triazin-2-amine hydrogen oxalate (**3**)*

From **3b** (0.36 g) and 2-chloro-4,6-dimethoxy-1,3,5-triazine (0.44 g), purification by column chromatography (eluent: EtOAc/$N(C_2H_5)_3$/petroleum ether; 95:5:100). Yield: 43%; $C_{13}H_{23}N_5O_2{\cdot}C_2H_2O_4{\cdot}0.2H_2O$ (375.0); b.p. 157.6–158.1 °C; ^{1}H-NMR (CF_3COOD) δ 7.16 (br, 1H, NH), 4.29 (s, 3H, OCH_3), 4.23 (s, 3H, OCH_3), 3.75–3.84 (m, 4H, C*H*$_2$NH, Pip-2,6H$_{eq}$), 3.38 (m, 2H, PipCH$_2$), 3.05 (m, 2H, Pip-2,6H$_{ax}$), 2.32 (m, 2H, PipCH$_2$C*H*$_2$), 1.88–2.13 (m, 5H, Pip-3,5H, Pip-4H$_{eq}$), 1.61 (m, 1H, Pip-4H$_{ax}$); EI-MS *m/z* (%) 281 ($M^{+\bullet}$, 7); C, H, N.

*N-Methyl-N-(2-piperidinoethyl)pyridin-4-amine trihydrochloride (**18**)*

From **18a** (0.52 g, 3.6 mmol) and 4-chloropyridine·HCl (0.38 g), purification by column chromatography (eluent: EtOAc/$N(C_2H_5)_3$; 95:5 → EtOAc/MeOH/$N(C_2H_5)_3$; 95:5:5). The residue was crystallized and recrystallized as salt of HCl from 2-propanol/Et_2O. Yield: 34%; $C_{13}H_{21}N_3{\cdot}3HCl{\cdot}H_2O$ (346.7); m.p. 146.5–147.1 °C; ^{1}H-NMR (CF_3COOD) δ 8.17 (d, *J* = 7.5 Hz, 2H, Py-2,6H), 7.08 (m, 2H, Py-3,5H), 4.22 (t, *J* = 8.2 Hz, 2H, C*H*$_2$NPy), 3.86 (m, 2H, Pip-2,6H$_{eq}$), 3.57 (t, *J* = 8.2 Hz, 2H, PipCH$_2$), 3.36 (s, 3H, NCH_3), 3.16 (m, 2H, Pip-2,6H$_{ax}$), 1.92δ2.15 (m, 5H, Pip-3,5H, Pip-4H$_{eq}$), 1.64 (m, 1H, Pip-4H$_{ax}$); EI-MS *m/z* (%) 219 ($M^{+\bullet}$, 2); C, H, N.

*N-Methyl-N-(4-piperidinobutyl)quinolin-4-amine dihydrogen oxalate (**19**)*

From **19b** (0.43 g) and 4-chloroquinoline·HCl (0.41 g). Yield: 42%; $C_{19}H_{27}N_3{\cdot}2C_2H_2O_4{\cdot}0.25H_2O$ (477.5); m.p. 135–136 °C; ^{1}H-NMR (CF_3COOD) δ 8.31 (d, *J* = 8.7 Hz, 1H, Quin-2H), 8.25 (d, *J* = 7.2 Hz, 1H, Quin-8H), 7.96–7.97 (m, 1H, Quin-6H), 7.90 (d, *J* = 8.3 Hz, 1H, Quin-5H), 7.71–7.75 (m, 1H, Quin-7H), 6.95 (d, *J* = 7.2 Hz, 1H, Quin-3H), 3.92–3.94 (m, 2H, C*H*$_2$NH), 3.75–3.78 (m, 2H, Pip-2,6H$_{eq}$), 3.62 (s, 3H, NCH_3), 3.32–3.33 (m, 2H, PipCH$_2$), 2.98–3.07 (m, 2H, Pip-2,6H$_{ax}$), 1.87–2.12 (m, 9H, Pip-3,5H, Pip-4H$_{eq}$, PipCH$_2$(C*H*$_2$)$_2$), 1.59–1.66 (m, 1H, Pip-4H$_{ax}$); EI-MS *m/z* (%) 297 ($M^{+\bullet}$, 14); C, H, N.

*N-Methyl-N-(5-piperidinopentyl)quinolin-4-amine dihydrogen oxalate (**20**)*

From **20c** (0.46 g) and 4-chloropyridine·HCl (0.38 g). Yield: 53%; $C_{20}H_{29}N_3{\cdot}2C_2H_2O_4{\cdot}0.25H_2O$ (491.5); m.p. 138–139 °C; ^{1}H-NMR (CF_3COOD) δ 8.32 (d, *J* = 8.6 Hz, 1H, Quin-2H), 8.22 (d, *J* = 7.4 Hz, 1H, Quin-8H), 7.95–7.98 (m, 1H, Quin-6H), 7.86 (d, *J* = 8.3 Hz, 1H, Quin-5H), 7.70–7.73 (m, 1H, Quin-7H), 6.92 (d, *J* = 7.4 Hz, 1H, Quin-3H), 3.89 (T, *J* = 7.8 Hz, 2H, C*H*$_2$NH), 3.67–3.81 (m, 2H, Pip-2,6H$_{eq}$), 3.62 (s, 3H, NCH_3), 3.22–3.28 (m, 2H, PipCH$_2$), 2.97–3.05 (m, 2H, Pip-2,6H$_{ax}$), 1.87–2.12 (m, 9H, Pip-3,5H, Pip-4H$_{eq}$, PipCH$_2$C*H*$_2$CH$_2$C*H*$_2$), 1.59–1.66 (m, 3H, Pip-4H$_{ax}$, Pip(CH$_2$)$_2$C*H*$_2$); EI-MS *m/z* (%) 311 ($M^{+\bullet}$, 21); C, H, N.

*General procedure for the preparation of compounds **4** and **6***

The corresponding ω-piperidinoalkanamine (5 mmol) and 2-chloro-5-nitropyridine (5 mmol), $N(C_2H_3)_3$ (5 mL), and a catalytic amount of KI were dissolved in EtOH (20 mL) and refluxed for 12 h. The solvent was removed under reduced pressure, the residue dissolved in EtOAc/H_2O and the organic layer washed several times with a sat. aqueous solution of K_2CO_3, followed by extraction with aqueous HCl (*c* = 2 mol/L). Subsequently, the aqueous layer was washed with EtOAc, basified, extracted with CH_2Cl_2, and concentrated *in vacuo*. The residue was purified by flash chromatography (eluent: CH_2Cl_2/$N(C_2H_5)_3$; 95:5).

*N-(3-Piperidinopropyl)-5-nitropyridin-2-amine dihydrogen oxalate (**4**)*

From **3b** (1.1 g). Yield: 53%; $C_{13}H_{20}N_4O_2{\cdot}1.6\ C_2H_2O_4$ (408.4); m.p. 152.4 °C; ^{1}H-NMR (CF_3COOD) δ 9.05 (s, 1H, Py-6H), 8.76 (m, 1H, Py-4H), 7.29 (d, *J* = 9.0 Hz, 1H, Py-3H), 3.77 (m, 4H, Pip-2,6H$_{eq}$, C*H*$_2$NHPy), 3.42 (t, *J* = 8.1 Hz, 2H, PipCH$_2$), 3.06 (m, 2H, Pip-2,6H$_{ax}$), 2.42 (m, 2H, PipCH$_2$C*H*$_2$), 1.88–2.14 (m, 5H, Pip-3,5H, Pip-4H$_{eq}$), 1.64 (m, 1H, Pip-4H$_{ax}$); EI-MS *m/z* (%) 264 ($M^{+\bullet}$, 7); C, H, N.

*N-(4-Piperidinobutyl)-5-nitropyridin-2-amine hydrogen oxalate (**6**)*

From **6b** (0.78 g). Yield: 59%; $C_{14}H_{22}N_4O_2{\cdot}C_2H_2O_4$ (368.4); m.p. 153.0–153.2 °C; ^{1}H-NMR δ 8.90 (s, 1H, Py-6H), 8.19 (d, 1H, Py-4H), 8.11* (s, 1H, NH), 6.56 (d, *J* = 9.4 Hz, 1H, Py-3H), 3.41 (m, 2H, C*H*$_2$NHPy), 2.95–2.99 (m, 6H, Pip-2,6H, PipCH$_2$), 1.53–1.70 (m, 10H, Pip-3,4,5H, PipCH$_2$(C*H*$_2$)$_2$); EI-MS *m/z* (%) 278 ($M^{+\bullet}$, 4); C, H, N.

*General procedure for the preparation of compounds **5**, **10**, and **17***

The corresponding nitropyridine derivative (base, 1 mmol) in dry THF (20 mL) was treated with Pd/C (10%, 50 mg) and hydrogen (1 bar) for 12 h. Then, the mixture was filtered and concentrated under reduced pressure.

N^2-(3-Piperidinopropyl)-2,5-pyridindiamine trihydrogen oxalate (*5*)

From **4** (0.26 g). The crude product was purified by flash chromatography (eluent: EtOAc/$N(C_2H_5)_3$/MeOH; 95:5:5). Yield: 55%; $C_{13}H_{22}N_4{\cdot}3C_2H_2O_4{\cdot}0.5H_2O$ (513.5); b.p. 138.9–139.1 °C; ^{1}H-NMR (CF_3COOD) δ 8.69 (s, 1H, Py-6H), 8.23 (d, *J* = 9.6 Hz, 1H, Py-4H), 7.22 (d, *J* = 9.6 Hz, 1H, Py-3H), 7.18 (br, 1H, NH), 3.78 (m, 2H, Pip-2,6H$_{eq}$), 3.68 (t, *J* = 6.2 Hz, 2H, C*H*$_2$NH), 3.41 (m, 2H, PipCH$_2$), 3.04 (m, 2H, Pip-2,6H$_{ax}$), 2.38 (m, 2H, PipCH$_2$C*H*$_2$), 1.89–2.14 (m, 5H, Pip-3,5H, Pip-4H$_{eq}$), 1.64 (m, 1H, Pip-4H$_{ax}$); EI-MS *m/z* (%) 234 ($M^{+\bullet}$, 9); C, H, N.

N^2-(5-Piperidinopentyl)-2,5-pyridindiamine dihydrogen oxalate (*10*)

From **8** (0.29 g). Yield: 75%; $C_{15}H_{26}N_4{\cdot}2C_2H_2O_4$ (442.5); m.p. 85.7–87.3 °C; ^{1}H-NMR δ 7.35 (s, 1H, Py-6H), 7.08 (d, *J* = 9.0 Hz, 1H, Py-4H), 6.54 (d, *J* = 9.0 Hz, 1H, Py-3H), 3.14 (m, 4H, C*H*$_2$NHPy, PipCH$_2$), 2.97 (m, 4H, Pip-2,6H), 1.31–1.71 (m, 12H, Pip-3,4,5H, PipCH$_2$(C*H*$_2$)$_3$); EI-MS *m/z* (%) 262 ($M^{+\bullet}$, 11); C, H, N.

N^2-(6-Piperidinohexyl)-2,5-pyridindiamine dihydrogen oxalate (*17*)

From **15** (0.31 g). Yield: 51%; $C_{16}H_{28}N_4{\cdot}2C_2H_2O_4{\cdot}0.25H_2O$ (461.0); m.p. 125.2–127.4 °C; ^{1}H-NMR (CF_3COOD) δ 8.28 (d, *J* = 7.6 Hz, 1H, Py-6H), 8.02 (d, *J* = 6.4 Hz, 1H, Py-4H),

7.11 (t, *J* = 6.5 Hz, 1H, Py-5H), 6.65 (br, 1H, NH), 3.72 (m, 2H, Pip-2,6H_{eq}), 3.63 (t, *J* = 6.6 Hz, 2H, CH_2NHPy), 3.21 (m, 2H, PipCH_2), 3.02 (m, 2H, Pip-2,6H_{ax}), 1.91–2.13 (m, 9H, Pip-3,5H, Pip-4H_{eq}, PipCH_2CH_2, C$H_2$$CH_2$NHPy), 1.35–1.63 (m, 5H, Pip-4H_{ax}, Pip$CH_2$$CH_2$(C$H_2$)$_2$); EI-MS *m/z* (%) 276 ($M^{+\bullet}$, 11); C, H, N.

*5-Piperidinopentanamine dihydrochloride (**20a**)*

5-Piperidinovaleronitrile (5.68 mL, 30 mmol) and freshly prepared Raney nickel catalyst in aqueous ammonia (ω = 25%, 100 mL) were stirred under hydrogen (p 10 bar) at r.t. for 20 h. The mixture was filtered, concentrated *in vacuo*, and the residue was purified by rotatory chromatography. It was crystallized with HCl from 2-propanol/Et_2O. Yield: 95%; $C_{10}H_{22}N_2$·2HCl (513.5); m.p. 185.6°C; ^{1}H-NMR δ 8.12* (s, 1H, NH), 3.36–3.39 (m, 2H, Pip-2,6H_{eq}), 2.91–2.97 (m, 2H, C$H_2$$NH_2$), 2.75–2.85 (m, 4H, Pip-2,6H_{ax}, PipCH_2), 1.68–1.87 (m, 7H, Pip-3,4,5H_{eq}, PipCH_2C$H_2$$CH_2CH_2$), 1.55–1.62 (m, 2H, C$H_2$-(C$H_2$)$_2$-$NH_2$), 1.30–1.41 (m, 3H, Pip-3,4,5H_{ax}); EI-MS *m/z* (%) 170 ($M^{+\bullet}$, 4).

*General procedure for the preparation of compounds **19a** and **20b***

Chloroformic acid benzyl ester (1.57 mL, 11 mmol) was added dropwise to the corresponding ω-piperidinoalkanamine (10 mmol) in aqueous NaOH (*c* = 2 mol/L, 10 mL) and THF (10 mL) under argon and ice-cooling. The mixture was stirred for 2 h at r.t. Then, the aqueous layer was extracted with EtOAc. The organic layers were combined, filtered, concentrated *in vacuo*, and the residue was purified by rotatory chromatography.

*4-Piperidinobutylcarbamic acid benzyl ester (**19a**)*

From 4-piperidinobutanamine (**6b**, 1.56 g). Yield: 72%; $C_{17}H_{26}N_2O_2$ (290.4); ^{1}H-NMR δ 7.22–7.38 (m, 5H, Ph-H), 5.00 (s, 2H, OCH_2), 2.99 (d, *J* = 5.6 Hz, 2H, CH_2NH), 2.27 (m, 4H, Pip-2,6H), 2.19 (t, *J* = 6.1 Hz, 2H, PipCH_2), 1.44–1.49 (m, 4H, PipCH_2(CH_2)$_2$), 1.35–1.40 (m, 6H, Pip-3,4,5H); FAB-MS *m/z* (%) 291 ($M^{+\bullet}$+$H^{+\bullet}$, 92).

*5-Piperidinopentylcarbamic acid benzyl ester (**20b**)*

From 5-piperidinopentanamine (**20a**, 1.70 g). Yield: 79%; $C_{17}H_{26}N_2O_2$ (290.4); ^{1}H-NMR δ 7.32–7.42 (m, 5H, Ph-H), 5.04 (s, 2H, OCH_2), 2.99–3.04 (m, 2H, CH_2NH), 2.30–2.36 (m, 4H, Pip-2,6H), 2.21 (t, *J* = 7.3 Hz, 2H, PipCH_2), 1.48–1.53 (m, 4H, PipCH_2C$H_2$$CH_2CH_2$), 1.40–1.45 (m, 6H, Pip-3,4,5H), 1.23–1.30 (m, 2H, Pip(CH_2)$_2$CH_2); FAB-MS *m/z* (%) 305 ($M^{+\bullet}$+$H^{+\bullet}$, 100).

*General procedure for the preparation of compounds **19b** and **20c***

Under argon and ice-cooling, the corresponding carbamate derivative (7 mmol) in THF (10 mL) was added dropwise to $LiAlH_4$ (0.88 g, 22 mmol) in THF (5 mL). After refluxing for 3 h, the mixture was treated with a sat. aqueous solution of sodium potassium tartrate (2 mL) and stirred for 1 h. The mixture was filtered, the filter residue washed with hot THF, the THF fractions unified and concentrated *in vacuo*. The residue was purified by rotatory chromatography.

*N-Methyl-4-piperidinobutanamine (**19b**)*

From **19a** (2.05 g, 7 mmol). Yield: 84%; $C_{10}H_{22}N_2$ (170.3); ^{1}H-NMR δ 3.16 (m, 2H, Pip-2,6H_{eq}), 2.44 (m, 2H, CH_2NH), 2.26 (m, 5H, Pip-2,6H_{ax}, NCH_3), 2.19 (t, *J* = 6.6 Hz, 2H, PipCH_2), 1.44–1.49 (m, 4H, PipCH_2(CH_2)$_2$), 1.37–1.42 (m, 6H, Pip-3,4,5H); EI-MS *m/z* (%) 170 ($M^{+\bullet}$, 5).

*N-Methyl-5-piperidinopentanamine (**20c**)*

From **20b** (2.40 g, 7.9 mmol). Yield: 85%; $C_{11}H_{24}N_2$ (184.3); ^{1}H-NMR δ 3.10 (m, 2H, Pip-2,6H_{eq}), 2.41 (t, *J* = 7.0 Hz, 2H, CH_2NH), 2.24–2.26 (m, 7H, Pip-2,6H_{ax}, NCH_3), 2.18 (t, *J* = 7.4 Hz, 2H, PipCH_2), 1.42–1.49 (m, 4H, PipCH_2C$H_2$$CH_2CH_2$), 1.34–1.41 (m, 6H, Pip-3,4,5H), 1.20–1.28 (m, 2H, Pip(CH_2)$_2$CH_2; EI-MS *m/z* (%) 184 ($M^{+\bullet}$, 3).

*General procedure for the preparation of compounds **7a**–**9a**, **12a**, and **16a***

The corresponding ω-aminoalkanol (11 mmol), aryl chloride (10 mmol), N(C_2H_5)$_3$ (5 mL), and a catalytic amount of KI were dissolved in EtOH (20 mL) and refluxed for 12 h. The mixture was concentrated under reduced pressure and the residue dissolved in EtOAc/H_2O. The organic layer was washed with sat. aqueous K_2CO_3 and extracted with aqueous HCl (*c* = 2 mol/L). Then, the aqueous layer was washed with EtOAc, basified, and extracted with CH_2Cl_2. After removal of the solvent *in vacuo* the crude product was purified by flash chromatography (eluent: EtOAc/N(C_2H_5)$_3$; 95:5).

*5-Amino-N-(3-nitropyridin-2-yl)pentanol (**7a**)*

From 5-aminopentanol (0.52 g, 5 mmol) and 2-chloro-3-nitropyridine (0.79 g, 5 mmol). Yield: 72%; $C_{10}H_{15}N_3O_3$ (225.3); ^{1}H-NMR δ 8.45–8.49 (m, 3H, Py-4,6H, NH) 6.72–6.75 (t, *J* = 8.4 Hz, 1H, Py-5H), 4.41 (br, 1H, OH), 3.56 (t, *J* = 6.8 Hz, 2H, CH_2OH), 3.38 (t, *J* = 6.3 Hz, 2H, CH_2NH), 1.61 (m, 2H, C$H_2$$CH_2$NH), 1.45 (m, 2H, HOC$H_2CH_2$), 1.35 (m, 2H, HO(C$H_2$)$_2CH_2$); EI-MS *m/z* (%) 225 ($M^{+\bullet}$, 8).

*5-Amino-N-(5-Nitropyridin-2-yl)pentanol (**8a**)*

From 5-aminopentanol (0.52 g, 5 mmol) and 2-chloro-5-nitropyridine (0.81 g, 5 mmol). Yield: 94%; $C_{10}H_{15}N_3O_3$ (225.3); ^{1}H-NMR δ 8.90 (s, 1H, Py-6H), 8.08–8.13 (m, 2H, Py-4H, NH), 6.54 (d, *J* = 9.4 Hz, 1H, Py-3H), 4.38 (br, 1H, OH), 3.40 (m, 4H, CH_2OH, CH_2NH), 1.56 (m, 2H, C$H_2$$CH_2$NH), 1.45 (m, 2H, HOC$H_2CH_2$), 1.36 (m, 2H, HO(C$H_2$)$_2CH_2$); EI-MS *m/z* (%) 225 ($M^{+\bullet}$, 14).

*5-Amino-N-(3,5-dinitropyridin-2-yl)pentanol (**9a**)*

From 5-aminopentanol (0.52 g, 5 mmol) and 2-chloro-3,5-dinitropyridine (1.02 g, 5 mmol) under ice-cooling. Yield: 99%; $C_{10}H_{14}N_4O_5$ (270.3); ^{1}H-NMR δ 9.31* (t, *J* = 5.5 Hz, 1H, NH), 9.25 (s, 1H, Py-4H), 8.96 (s, 1H, Py-6H), 3.66 (t, *J* = 6.7 Hz, 2H, CH_2OH), 3.39 (m, 2H, CH_2NH), 1.63 (m, 2H, C$H_2$$CH_2$NH), 1.45 (m, 2H, HOC$H_2CH_2$), 1.35 (m, 2H, HO(C$H_2$)$_2CH_2$); EI-MS *m/z* (%) 270 ($M^{+\bullet}$, 3).

*6-Amino-N-quinolin-2-ylhexanol (**12a**)*

From 6-aminohexanol (1.29 g) and 2-chloroquinoline (1.63 g). Yield: 24%; $C_{15}H_{20}N_2O$ (244.3); ^{1}H-NMR δ 7.80 (d, *J* = 8.9 Hz, 1H, Quin-4H), 7.57 (d, *J* = 8.9 Hz, 1H, Quin-8H), 7.43–7.46 (m, 2H, Quin-5,7H), 7.11 (m, 1H, Quin-6H), 6.94*

(t, *J* = 5.2 Hz, NH), 6.74 (d, *J* = 8.9 Hz, Quin-3H), 3.34–3.41 (m, 4H, C*H*$_2$OH, C*H*$_2$NH), 1.57 (m, 2H, C*H*$_2$CH$_2$NH), 1.33–1.45 (m, 6H, HOCH$_2$(C*H*$_2$)$_3$); EI-MS *m/z* (%) 244 (M$^{+\bullet}$, 30).

*6-Amino-N-(5-nitropyridin-2-yl)hexanol (**16a**)*

From 6-aminohexanol (1.29 g) and 2-chloro-5-nitropyridine (1.62 g). Yield: 66%; $C_{11}H_{17}N_3O_3$ (239.3); ^{1}H-NMR δ 8.90 (s, 1H, Py-6H), 8.12 (m, 2H, Py-4H, NH), 6.54 (d, *J* = 9.4 Hz, 1H, Py-3H), 4.33 (br, 1H, OH), 3.37 (m, 4H, C*H*$_2$OH, C*H*$_2$NH), 1.54 (m, 2H, C*H*$_2$CH$_2$NH), 1.31–1.41 (m, 6H, HOCH$_2$(C*H*$_2$)$_3$); EI-MS *m/z* (%) 239 (M$^+$, 13).

*General procedure for the preparation of compounds **11a** and **13a–15a***

The corresponding ω-aminoalkanol (11 mmol), aryl chloride (10 mmol), phenol (3 g, 31.9 mmol) were stirred for 12 h at 140 °C. After cooling, aqueous NaOH (*c* = 6 mol/L) and EtOAc were added and the mixture stirred for 1 h at r.t. After washing with aqueous NaOH, the organic layer was extracted with aqueous HCl (*c* = 5 mol/L). The aqueous layer was washed with EtOAc, basified, and extracted with CH_2Cl_2. Then, the organic layer was concentrated *in vacuo*.

*6-Amino-N-(benzo[d][1,3]thiazol-2-yl)hexanol (**11a**)*

From 6-aminohexanol (1.29 g) und 2-chlorobenzo[d][1,3]thiazole (1.69 g). The crude product was purified by flash chromatography (eluent: CH_2Cl_2/MeOH; 95:5 → 90:10). Yield: 65%; $C_{13}H_{18}N_2OS$ (250.4); ^{1}H-NMR δ 7.78 (d, *J* = 7.8 Hz, 1H, Benz-4H), 7.51 (d, *J* = 8.1 Hz, 1H, Benz-7H), 7.35 (m, 1H, Benz-5H), 7.17 (m, 1H, Benz-6H), 3.47 (t, *J* = 6.4 Hz, 2H, C*H*$_2$OH), 3.38 (t, *J* = 6.4 Hz, 2H, C*H*$_2$NH), 1.63 (m, 2H, C*H*$_2$CH$_2$NH), 1.31–1.45 (m, 6H, HOCH$_2$(C*H*$_2$)$_3$); EI-MS *m/z* (%) 250 (M$^{+\bullet}$, 36).

*6-Amino-N-pyrimidin-2-ylhexanol (**13a**)*

From 6-aminohexanol (1.29 g, 11 mmol) and 2-chloropyrimidine (1.14 g, 10 mmol). The crude product was purified by flash chromatography (eluent: CH_2Cl_2/NH$_3$-sat. MeOH; 95:5). Yield: 30%; $C_{10}H_{17}N_3O$ (195.3); ^{1}H-NMR δ 8.22 (t, *J* = 4.7 Hz, 2H, Pyr-4,6H), 7.07* (s, 1H, NH), 6.50 (t, *J* = 4.7 Hz, 1H, Pyr-5H), 3.37 (t, *J* = 6.4 Hz, 2H, HOC*H*$_2$), 3.21 (m, 2H, C*H*$_2$NH), 1.27–1.51 (m, 8H, HOCH$_2$(C*H*$_2$)$_4$); EI-MS *m/z* (%) 195 (M$^{+\bullet}$, 19).

*6-Amino-N-pyridin-4-ylhexanol (**14a**)*

From 6-aminohexanol (1.29 g), 4-chloropyridine hydrochloride (1.5 g), and N(C$_2$H$_5$)$_3$ (5 mL). The crude product was purified by flash chromatography (eluent: EtOAc/N(C$_2$H$_5$)$_3$/MeOH; 95:5:4). Yield: 55%; $C_{11}H_{18}N_2O$ (194.3); ^{1}H-NMR δ 8.04 (d, *J* = 5.7 Hz, 2H, Py-2,6H), 6.50 (m, 3H, Py-3,5H, NH), 3.43 (m, 2H, CH$_2$OH), 3.07 (t, *J* = 6.9 Hz, 2H, C*H*$_2$NH), 1.56–1.59 (m, 2H, C*H*$_2$CH$_2$NH), 1.44–1.49 (m, 2H, HOCH$_2$C*H*$_2$), 1.35–1.43 (m, 4H, HOCH$_2$CH$_2$(C*H*$_2$)$_2$); EI-MS *m/z* (%) 194 (M$^{+\bullet}$, 10).

*6-Amino-N-(3-nitropyridin-2-yl)hexanol (**15a**)*

From 6-aminohexanol (1.29 g) and 2-chloro-3-nitropyridine (1.58 g). Yield: 58%; $C_{11}H_{17}N_3O_3$ (239.3); ^{1}H-NMR δ 8.39–8.48 (m, 3H, Py-4,6H, NH) 6.72–6.75 (m, 1H, Py-5H), 3.56 (t, *J* = 6.4 Hz, 2H, C*H*$_2$OH), 3.38 (t, *J* = 6.4 Hz, 2H, C*H*$_2$NH), 1.57–1.62 (m, 2H, C*H*$_2$CH$_2$NH), 1.30–1.43 (m, 6H, HOCH$_2$(C*H*$_2$)$_3$); EI-MS *m/z* (%) 239 (M$^{+\bullet}$, 1).

*General procedure for the preparation of compounds **7b–9b** and **11b–16b***

To a solution of the corresponding *N*-substituted ω-aminoalkanol (3 mmol) in dry THF (20 mL), $SOCl_2$ (0.59 g, 5 mmol) was added under ice-cooling. The mixture was stirred 2 h at 50 °C and excess $SOCl_2$ was removed under reduced pressure.

*N-(5-Chloropentyl)-3-nitropyridin-2-amine hydrochloride (**7b**)*

From **7a** (0.68 g). Yield: 96%; $C_{10}H_{14}ClN_3O_2$·HCl (280.2); ^{1}H-NMR δ 8.41–8.52 (m, 3H, Py-4,6H, NH) 6.74–6.78 (m, 1H, Py-5H), 3.59–3.67 (m, 4H, ClCH$_2$, C*H*$_2$NH), 1.74–1.81 (m, 2H, C*H*$_2$CH$_2$NH), 1.63–1.66 (m, 2H, ClCH$_2$C*H*$_2$), 1.42–1.49 (m, 2H, ClCH$_2$CH$_2$C*H*$_2$); EI-MS *m/z* (%) 243 (M$^{+\bullet}$, 10).

*N-(5-Chloropentyl)-5-nitropyridin-2-amine hydrochloride (**8b**)*

From **8a** (0.68 g). Yield: 91%; $C_{10}H_{14}ClN_3O_2$·HCl (280.2); ^{1}H-NMR δ 8.89 (s, 1H, Py-6H), 8.20–8.40* (s, 1H, NH), 8.10 (d, *J* = 6.8 Hz, 1H, Py-4H), 6.61–6.64 (d, *J* = 6.8 Hz, 1H, Py-3H), 3.64 (t, *J* = 6.6 Hz, 2H, CH$_2$Cl), 3.40 (m, 2H, C*H*$_2$NH), 1.75 (m, 2H, C*H*$_2$CH$_2$NH), 1.58 (m, 2H, ClCH$_2$C*H*$_2$), 1.45 (m, 2H, ClCH$_2$CH$_2$C*H*$_2$); EI-MS *m/z* (%) 243 (M$^{+\bullet}$, 11).

*N-(5-Chloropentyl)-3,5-dinitropyridin-2-amine hydrochloride (**9b**)*

From **9a** (0.76 g). Yield: 95%; $C_{10}H_{13}ClN_4O_4$·HCl (325.1); ^{1}H-NMR δ 9.31* (s, 1H, NH), 9.24 (s, 1H, Py-4H), 8.96 (s, 1H, Py-6H), 3.62–3.68 (m, 4H, CH$_2$Cl, C*H*$_2$NH), 1.72–1.77 (m, 2H, C*H*$_2$CH$_2$NH), 1.62–1.67 (m, 2H, ClCH$_2$C*H*$_2$), 1.42–1.48 (m, 2H, ClCH$_2$CH$_2$C*H*$_2$); EI-MS *m/z* (%) 288 (M$^{+\bullet}$, 10).

*N-(6-Chlorohexyl)-benzo[d][1,3]thiazol-2-amine hydrochloride (**11b**)*

From **11a** (1.25 g, 5 mmol). Yield: 72%; $C_{13}H_{17}ClN_2S$·HCl (305.3); ^{1}H-NMR δ 7.82 (d, *J* = 7.9 Hz, 1H, Benz-4H), 7.52 (d, *J* = 8.0 Hz, 1H, Benz-7H), 7.38 (m, 1H, Benz-5H), 7.21 (m, 1H, Benz-6H), 3.64 (t, *J* = 6.6 Hz, 2H, CH$_2$Cl), 3.48 (m, 2H, C*H*$_2$NH), 1.70–1.75 (m, 2H, C*H*$_2$CH$_2$NH), 1.61–1.68 (m, 2H, ClCH$_2$C*H*$_2$), 1.38–1.45 (m, 4H, ClCH$_2$CH$_2$(C*H*$_2$)$_2$); EI-MS *m/z* (%) 268 (M$^{+\bullet}$, 31).

*N-(6-Chlorohexyl)-quinolin-2-amine hydrochloride (**12b**)*

From **12a** (0.73 g). Yield: 99%; $C_{15}H_{19}ClN_2$·HCl (298.3); ^{1}H-NMR δ 7.80 (d, *J* = 8.9 Hz, 1H, Quin-4H), 7.58 (d, *J* = 7.8 Hz, 1H, Quin-8H), 7.41–7.48 (m, 2H, Quin-5,7H), 7.11 (t, *J* = 6.7 Hz, 1H, Quin-6H), 6.96* (s, 1H, NH), 6.74 (d, *J* = 8.9 Hz, Quin-3H), 3.64 (t, *J* = 6.6 Hz, 2H, CH$_2$Cl), 3.38 (t, *J* = 6.4 Hz, 2H, C*H*$_2$NH), 1.72–1.75 (m, 2H, C*H*$_2$CH$_2$NH), 1.57–1.61 (m, 2H, ClCH$_2$C*H*$_2$), 1.39–1.44 (m, 4H, ClCH$_2$CH$_2$(C*H*$_2$)$_2$); EI-MS *m/z* (%) 262 (M$^{+\bullet}$, 19).

*N-(6-Chlorohexyl)-pyrimidin-2-amine hydrochloride (**13b**)*

From **13a** (0.54 g). Yield: 95%; $C_{10}H_{16}ClN_3$·HCl (249.2); ^{1}H-NMR δ 8.22 (t, *J* = 4.7 Hz, 2H, Pyr-4,6H), 7.06* (t, *J* = 5.4 Hz, 1H, NH), 6.51 (t, *J* = 4.7 Hz, 1H, Pyr-5H), 3.62 (t, *J* = 6.6 Hz, 2H, ClCH$_2$), 3.20–3.26 (m, 2H, C*H*$_2$NH), 1.67–1.74 (m,

2H, CH_2CH$_2$NH), 1.47–1.54 (m, 2H, ClCH$_2$CH_2), 1.29–1.43 (m, 4H, ClCH$_2$CH$_2$(CH_2)$_2$); EI-MS *m/z* (%) 213 ($M^{+\bullet}$, 11).

*N-(6-Chlorohexyl)-3-nitropyridin-2-amine hydrochloride (**15b**)*

From **15a** (0.67 g). Yield: 96%; $C_{11}H_{16}ClN_3O_2$·HCl (294.2); ^{1}H-NMR δ 8.39–8.48 (m, 3H, Py-4,6H, NH) 6.72–6.75 (m, 1H, Py-5H), 3.62 (t, *J* = 6.6 Hz, 2H, CH$_2$Cl), 3.57 (t, *J* = 7.0 Hz, 2H, CH_2NH), 1.72 (m, 2H, CH_2CH$_2$NH), 1.61 (m, 2H, ClCH$_2$CH_2), 1.32–1.44 (m, 4H, ClCH$_2$CH$_2$(CH_2)$_2$); EI-MS *m/z* (%) 257 ($M^{+\bullet}$, 8).

*N-(6-Chlorohexyl)-pyridin-4-amine hydrochloride (**14b**)*

From **14a** (0.58 g). Yield: 96%; $C_{11}H_{17}ClN_2$·HCl (249.2); ^{1}H-NMR δ 8.79* (s, 1H, NH), 8.19 (d, *J* = 6.7 Hz, 1H, Py-2H), 8.04 (d, *J* = 6.8 Hz, 1H, Py-6H), 6.92 (d, *J* = 6.7 Hz , 1H, Py-3H) 6.85 (d, *J* = 6.7 Hz, 1H, Py-5H), 3.63 (t, *J* = 6.6 Hz, 2H, CH$_2$Cl), 3.24 (t, *J* = 6.6 Hz, 2H, CH_2NH), 1.70–1.74 (m, 2H, CH_2CH$_2$NH), 1.55–1.59 (m, 2H, ClCH$_2$CH_2), 1.37–1.40 (m, 4H, ClCH$_2$CH$_2$(CH_2)$_2$); EI-MS *m/z* (%) 212 ($M^{+\bullet}$, 9).

*N-(6-Chlorohexyl)-5-nitropyridin-2-amine hydrochloride (**16b**)*

From **16a** (0.67 g). Yield: 90%; $C_{11}H_{16}ClN_3O_2$·HCl (294.2); ^{1}H-NMR δ 8.89 (s, 1H, Py-6H), 8.27* (s, 1H, NH), 8.08 (d, *J* = 6.8 Hz, 1H, Py-4H), 6.57–6.60 (d, *J* = 6.8 Hz, 1H, Py-3H), 3.62 (t, *J* = 6.5 Hz, 2H, CH$_2$Cl), 3.37 (m, 2H, CH_2NH), 1.71 (m, 2H, CH_2CH$_2$NH), 1.55 (m, 2H, ClCH$_2$CH_2), 1.35–1.41 (m, 4H, ClCH$_2$CH$_2$(CH_2)$_2$); EI-MS *m/z* (%) 257 ($M^{+\bullet}$, 10).

*General procedure for the preparation of compounds **7**–**9** and **11**–**16***

The corresponding *N*-substituted ω-chloroalkanamine (3 mmol), piperidine (2 mL, 20 mmol), K_2CO_3 (1.29 g, 9 mmol), and a catalytic amount of KI in EtOH (20 mL) were refluxed for 12 h. After removal of the solvent *in vacuo,* the residue was dissolved in EtOAc/H_2O and the organic layer washed with sat. aqueous K_2CO_3. The organic solvent was removed under reduced pressure and the residue purified by column chromatography (eluent: EtOAc/N(C_2H_5)$_3$/MeOH; 95:5:2).

*N-(5-Piperidinopentyl)-3-nitropyridin-2-amine hydrogen oxalate (**7**)*

From **7b** (0.83 g). Eluent: CH_2Cl_2 → CH_2Cl_2/NH_3-sat. MeOH (95:5).Yield: 22%; $C_{15}H_{24}N_4O_2$·$C_2H_2O_4$·0.25H_2O (386.9); m.p. 148.5–149.2 °C; ^{1}H-NMR (CF$_3$COOD) δ 9.14 (d, *J* = 8.1 Hz, 1H, Py-6H), 8.36 (d, *J* = 6.3 Hz, 1H, Py-4H), 7.22 (dd, $J_{4H/5H}$ = 6.4 Hz, $J_{5H/6H}$ = 8.0 Hz, 1H, Py-5H), 6.75 (br, 1H, NH) 3.76 (m, 4H, Pip-2,6H$_{eq}$, CH_2NHPy), 3.25 (m, 2H, PipCH$_2$) 3.00 (m, 2H, Pip-2,6H$_{ax}$), 1.87–2.04 (m, 9H, Pip-3,5H, Pip-4H$_{eq}$, PipCH$_2$CH_2CH$_2$CH_2), 1.64 (m, 3H, Pip-4H$_{ax}$, Pip(CH$_2$)$_2$CH_2); EI-MS *m/z* (%) 292 ($M^{+\bullet}$, 1); C, H, N.

*N-(5-Piperidinopentyl)-5-nitropyridin-2-amine hydrogen oxalate (**8**)*

From **8b** (0.84 g). The EtOAc layer was extracted with aqueous HCl (*c* = 2 mol/L). The aqueous layer was washed with EtOAc, basified, and extracted with CH_2Cl_2. Subsequently, the solvent was removed under reduced pressure. Yield: 45%; $C_{15}H_{24}N_4O_2$·$C_2H_2O_4$ (382.4); m.p. 95.7–96.0 °C; ^{1}H-NMR δ 8.90 (s, 1H, Py-6H), 8.20* (s, 1H, NH), 8.09 (d, *J* = 9.4 Hz, 1H, Py-4H), 6.55 (d, *J* = 9.4 Hz, 1H, Py-3H), 3.39 (m, 2H, CH_2NHPy), 2.94–2.98 (m, 6H, Pip-2,6H, PipCH$_2$), 1.31–1.71 (m, 12H, Pip-3,4,5H, PipCH$_2$(CH_2)$_3$); EI-MS *m/z* (%) 292 ($M^{+\bullet}$, 2); C, H, N.

*N-(5-Piperidinopentyl)-3,5-dinitropyridin-2-amine hydrogen oxalate (**9**)*

From **9b** (0.97 g). Eluent: EtOAc/N(C_2H_5)$_3$ (95:5). Yield: 13%; $C_{15}H_{23}N_5O_4$·$C_2H_2O_4$ (427.4); m.p. 131.4 °C; ^{1}H-NMR (CF$_3$COOD) δ 9.66 (s, 1H, Py-6H), 9.38 (s, 1H, Py-4H), 6.77 (br, 1H, NH), 3.90 (m, 2H, CH_2NHPy), 3.73 (m, 2H, Pip-2,6H$_{eq}$), 3.24 (m, 2H, PipCH$_2$), 2.97–3.06 (m, 2H, Pip-2,6H$_{ax}$), 1.91–2.13 (m, 9H, Pip-3,5H, Pip-4H$_{eq}$, PipCH$_2$CH_2CH$_2$CH_2), 1.63 (m, 3H, Pip-4H$_{ax}$, Pip(CH$_2$)$_2$CH_2); EI-MS *m/z* (%) 337 ($M^{+\bullet}$, 1); C, H, N.

*N-(6-Piperidinohexyl)-benzo[d][1,3]thiazol-2-amine dihydrogen oxalate (**11**)*

From **11b** (0.89 g). Eluent: CH_2Cl_2 → CH_2Cl_2/NH_3-sat. MeOH). Yield: 75%; $C_{18}H_{27}N_3S$·1.9$C_2H_2O_4$ (488.6); m.p. 98.5–101.8 °C; ^{1}H-NMR (CF$_3$COOD) δ 7.75 (d, *J* = 8.0 Hz, 1H, Benz-4H), 7.61 (dd, *J* = 7.5–7.7 Hz, 1H, Benz-5H), 7.56 (d, *J* = 8.0 Hz, 1H, Benz-7H), 7.49 (dd, *J* = 7.5–7.8 Hz, 1H, Benz-6H), 6.69 (br, 1H, NH), 3.72–3.75 (m, 2H, Pip-2,6H$_{eq}$), 3.61 (m, 2H, CH_2NHBenz), 3.24 (m, 2H, PipCH_2), 3.00 (m, 2H, Pip-2,6H$_{ax}$), 1.90–2.13 (m, 9H, Pip-3,5H, Pip-4H$_{eq}$, PipCH$_2$CH_2(CH$_2$)$_2$CH_2), 1.46–1.66 (m, 5H, Pip-4H$_{ax}$, PipCH$_2$CH$_2$(CH_2)$_2$); EI-MS *m/z* (%) 317 ($M^{+\bullet}$, 7); C, H, N.

*N-(6-Piperidinohexyl)quinolin-2-amine dihydrogen oxalate (**12**)*

From **12b** (0.75 g). Eluent: EtOAc/N(C_2H_5)$_3$ (95:5). Yield: 45%; $C_{20}H_{29}N_3$·2$C_2H_2O_4$·0.75H_2O (505.1); m.p. 90.7–91.5 °C; ^{1}H-NMR δ 7.92 (d, *J* = 9.0 Hz, 1H, Quin-4H), 7.65 (d, *J* = 7.8 Hz, 1H, Quin-8H), 7.50–7.56 (m, 2H, Quin-5,7H), 7.19 (t, *J* = 7.1 Hz, 1H, Quin-6H), 6.84 (d, *J* = 9.0 Hz, Quin-3H), 3.42 (m, 4H, Pip-2,6H$_{eq}$, CH_2NHQuin), 2.95–3.00 (m, 4H, Pip-2,6H$_{ax}$, PipCH$_2$), 1.58–1.71 (m, 9H, Pip-3,5H, Pip-4H$_{eq}$, PipCH$_2$CH_2(CH$_2$)$_2$CH_2), 1.34–1.44 (m, 5H, Pip-4H$_{ax}$, PipCH$_2$CH$_2$(CH_2)$_2$); EI-MS *m/z* (%) 311 ($M^{+\bullet}$, 7); C, H, N.

*N-(6-Piperidinohexyl-pyrimidin-2-amine hydrogen oxalate (**13**)*

From **13b** (0.67 g). Eluent: CH_2Cl_2 → CH_2Cl_2/NH_3-sat. MeOH). Yield: 47%; $C_{15}H_{26}N_4$·$C_2H_2O_4$ (352.4); m.p. 150.3–150.9 °C; ^{1}H-NMR δ 8.23 (t, *J* = 4.8 Hz, 2H, Pyr-4,6H), 7.09* (t, *J* = 5.6 Hz, 1H, NH), 6.55 (t, *J* = 4.8 Hz, 1H, Pyr-5H), 3.24 (t, *J* = 6.6 Hz, 2H, CH_2NHPyr), 2.91–3.21 (m, 6H, Pip-2,6H, PipCH$_2$), 1.30–1.70 (m, 14H, Pip-3,4,5H, PipCH$_2$(CH_2)$_4$); EI-MS *m/z* (%) 262 ($M^{+\bullet}$, 2); C, H, N.

*N-(6-Piperidinohexyl)pyridin-4-amine dihydrochloride (**14**)*

From **14b** (0.74 g). Eluent: EtOAc/N(C_2H_5)$_3$/MeOH (95:5:2). The crude product was crystallized with hydrochloric acid from 2-propanol/Et_2O. Yield: 92%; $C_{16}H_{27}N_3$·2HCl·0.5H_2O (343.3); m.p. 100.3–103.8 °C; ^{1}H-NMR δ 8.16 (d, *J* = 6.2 Hz, 2H, Py-2,6H), 7.36 (s, 1H, NH), 7.04 (d, *J* = 6.2 Hz , 2H, Py-3,5H), 3.89 (m, 2H, Pip-2,6H$_{eq}$), 3.59 (t, *J* = 6.6 Hz, 2H, CH_2NHPy), 3.36 (m, 2H, PipCH$_2$), 3.13 (m, 2H, Pip-2,6H$_{ax}$), 1.97–2.20 (m, 9H, Pip-3,5H, Pip-4H$_{eq}$, PipCH$_2$CH_2-(CH$_2$)$_2$CH_2), 1.71 (m, 5H, Pip-4H$_{ax}$, PipCH$_2$CH$_2$(CH_2)$_2$CH$_2$); EI-MS *m/z* (%) 261 ($M^{+\bullet}$, 6); C, H, N.

*N-(6-Piperidinohexyl)-3-nitropyridin-2-amine hydrogen oxalate (**15**)*

From **15b** (0.78 g). Yield: 37%; $C_{16}H_{26}N_4O_2 \cdot C_2H_2O_4$ (396.4); m.p. 130.3–130.7°C; ^{1}H-NMR δ 8.47* (s, 1H, NH) 8.42 (dd, $J_{4H/5H}$ = 8.2 Hz, $J_{5H/6H}$ = 8.2 Hz, 2H, Py-4,6H), 6.75 (t, J = 8.2 Hz, 1H, Py-5H), 3.56 (t, J = 6.5 Hz, 2H, CH_2NHPy), 3.05 (m, 4H, Pip-2,6H), 2.92 (t, J = 8.2 Hz, 2H, PipCH_2), 1.58–1.71 (m, 10H, Pip-3,4,5H, PipCH_2CH_2(CH_2)$_2$CH_2), 1.32–1.36 (m, 4H, PipCH_2CH_2(CH_2)$_2$); EI-MS *m/z* (%) 306 ($M^{+\bullet}$, 1); C, H, N.

*N-(6-Piperidinohexyl)-5-nitropyridin-2-amine hydrogen oxalate (**16**)*

From **16b** (0.88 g). Yield: 55%; $C_{16}H_{26}N_4O_2 \cdot C_2H_2O_4$ (396.4); m.p. 118.6–119.7°C; ^{1}H-NMR δ 8.90 (s, 1H, Py-6H), 8.18* (s, 1H, NH), 8.08 (d, J = 9.4 Hz, 1H, Py-4H), 6.55 (d, J = 9.4 Hz, 1H, Py-3H), 3.41 (m, 2H, CH_2NHPy), 2.90–3.05 (m, 6H, Pip-2,6H, PipCH_2), 1.51–1.72 (m, 10H, Pip-3,4,5H, PipCH_2CH_2(CH_2)$_2$CH_2), 1.30–1.33 (m, 4H, PipCH_2CH_2-(CH_2)$_2$); EI-MS *m/z* (%) 306 ($M^{+\bullet}$, 1); C, H, N.

Pharmacology

[^{125}I]Iodoproxyfan binding assay

All new compounds were investigated in a histamine H_3 receptor-specific radioligand binding assay [40] with the exception of **3** and **13**. In brief, stably transfected CHO-K1 cells were washed and harvested with a PBS medium. They were centrifuged (140 g, 10 min, 4°C) and then homogenized with a Polytron in the ice-cold binding buffer (Na_2HPO_4/KH_2PO_4, c = 50 mmol/L, pH 7.5). The homogenate was centrifuged (23,000 × g, 30 min, 4°C) and the pellet obtained was resuspended in the binding buffer to constitute the membrane preparation used for the binding assays. Aliquots of the membrane suspension (5–15 μg protein) were incubated (60 min, 25°C) with [^{125}I]iodoproxyfan (c = 25 pmol/L) alone, or together with competing drugs dissolved in the same buffer (final volume: 200 μL). Incubations were performed in triplicate and stopped by four additions (5 mL) of ice-cold medium, followed by rapid filtration through glass microfiber filters (GF/B Whatman, Clifton, NJ, USA) presoaked in polyethylene imine (ω = 0.3%). Radioactivity trapped on the filters was measured with a LKB (Rockville, MD, USA) gamma counter (efficiency: 82%). Specific binding was defined as that inhibited by the specific H_3 receptor agonist imetit [40] (c = 1 μmol/L). The corresponding K_i values were determined according to the Cheng-Prusoff equation [41]. Data are presented as the mean of experiments performed at least in triplicate (n = 3–8).

Histamine H_3 receptor antagonist potency in vitro on synaptosomes of the rat cerebral cortex

Compound **13** was investigated for its antagonist potency by an *in vitro* method based on induction of [^{3}H]histamine release from rat synaptosomes by K^+-evoked depolarization [34]. The synaptosomal fraction, prepared according to Whittaker [42], was preincubated with L-[^{3}H]histidine (c = 0.4 μmol/L, 37°C, 30 min) in a modified Krebs-Ringer solution, washed extensively, and transferred into a fresh Krebs-Ringer buffer containing K^+ (c = 2 mmol/L). Compounds alone or together with histamine (c = 1 μmol/L) were added 5 min before the depolarization stimulus (final K^+ concentration: c = 30 mmol/L). Incubation was terminated by rapid centrifugation. [^{3}H]-Histamine levels were determined after ion-exchange chromatography by liquid scintillation spectrometry [34]. K_i values were calculated according to Cheng and Prusoff [41]. Data are presented as mean of experiments performed at least in triplicate.

Inhibition of histamine N-methyltransferase (HMT)

As described in Apelt et al. [30], all new compounds were assessed for their inhibitory potencies of rat kidney HMT activity. Briefly, after isolation of HMT from rat kidneys, the enzyme was purified according to Bowsher et al. [43] with minor modification [44]. At 37°C the compounds were incubated in a phosphate buffer (c = 20 mmol/L, pH 8.0) in different concentrations together with histamine (c = 1 μmol/L, final concentration) and *S*-adenosyl-L-methionine (c = 20 μmol/L, final concentration) in the presence of HMT. The reaction was stopped after 20 min by addition of ice-cold perchloric acid (c = 0.4 mol/L, final concentration). The N^τ-methylhistamine produced was measured by a specific enzyme-immunoassay. From the curve [concentration of inhibitor · N^τ-methylhistamine concentration] the IC_{50} value for each compound was calculated. HMT inhibition was investigated at least in triplicate for each compound. Values are given as mean with standard error of the mean (SEM).

References

[1] S. J. Hill, C. R. Ganellin, H. Timmerman, J.-C. Schwartz, N. P. Shankley, J. M. Young, W. Schunack, R. Levi, H. L. Haas, *Pharmacol. Rev.* **1997**, *49*, 253–278.

[2] T. Nakamura, H. Itadani, Y. Hidaka, M. Ohta, K. Tanaka, *Biochem. Biophys. Res. Commun.* **2000**, *279*, 615–620.

[3] J.-M. Arrang, M. Garbarg, J.-C. Schwartz, *Nature (London)* **1983**, *302*, 832–837.

[4] T. W. Lovenberg, B. L. Roland, S. J. Wilson, X. Jiang, J. Pyati, A. Huvar, M. R. Jackson, M. G. Erlander, *Mol. Pharmacol.* **1999**, *55*, 1101–1107.

[5] T. W. Lovenberg, J. Pyati, H. Chang, S. J. Wilson, M. G. Erlander, *J. Pharmacol. Exp. Ther.* **2000**, *293*, 771–778.

[6] P. L. Chazot, V. Hann, C. Wilson, G. Lees, C. L. Thompson, *Neuroreport* **2001**, *12*, 259–262.

[7] J. Tardivel-Lacombe, A. Rouleau, A. Heron, S. Morisset, C. Pillot, V. Cochois, J.-C. Schwartz, J.-M. Arrang, *Neuroreport* **2000**, *11*, 755–759.

[8] B. B. Yao, R. Sharma, S. Cassar, T. A. Esbenshade, A. A. Hancock, *Eur. J. Pharmacol.* **2003**, *482*, 49–60.

[9] H. Stark, W. Sippl, X. Ligneau, J.-M. Arrang, C. R. Ganellin, J.-C. Schwartz, W. Schunack, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 951–954.

[10] S. Morisset, A. Rouleau, X. Ligneau, F. Gbahou, J. Tardivel-Lacombe, H. Stark, W. Schunack, C. R. Ganellin, J.-C. Schwartz, J.-M. Arrang, *Nature (London)* **2000**, *408*, 860–864.

[11] J.-M. Arrang, M. Garbarg, J.-C. Lancelot, J.-M. Lecomte, H. Pollard, M. Robba, W. Schunack, J.-C. Schwartz, *Nature (London)* **1987**, *327*, 117–123.

[12] J.-M. Arrang, M. Garbarg, J.-C. Schwartz, *Neuroscience* **1985**, *15*, 553-562; J.-M. Arrang, M. Garbarg, J.-C. Schwartz, *Neuroscience* 1987, *23*, 149–157.

[13] J.-C. Schwartz, J.-M. Arrang, M. Garbarg, H. Pollard, M. Ruat, *Physiol. Rev.* **1991**, *71*, 1–51.

[14] R. Leurs, R. C. Vollinga, H. Timmerman, *Prog. Drug Res*. **1995**, *45*, 107–165.

[15] R. A. Bakker, H. Timmerman, R. Leurs, *Clin. Allergy Immunol.* **2002**, *17,* 27–64.

[16] H. Stark, J.-M. Arrang, X. Ligneau, M. Garbarg, C. R. Ganellin, J.-C. Schwartz, W. Schunack, *Prog. Med. Chem.* **2001**, *38*, 279–308.

[17] H. Stark, *Expert Opin. Ther. Patents* **2003**, *13*, 851–865.

[18] S. Graßmann, B. Sadek, X. Ligneau, S. Elz, C. R. Ganellin, J.-M. Arrang, J.-C. Schwartz, H. Stark, W. Schunack, *Eur. J. Pharm. Sci.* **2002**, *15*, 367–378.

[19] P. Panula, K. Kuokkanen, M. Relja, K. S. Eriksson, T. Sallmen, J. O. Rinne, H. Kalimo, *Soc. Neurosci. Abstr.* **1995**, *21*, 1977.

[20] S. Morisset, E. Traiffort, J.-C. Schwartz, *Eur. J. Pharmacol.* **1996**, *315*, R1–2.

[21] S. Miyazaki, M. Imaizumi, K. Onodera, *Life Sci.* **1995**, *57*, 2137–2144; P. Blandina, M. Giorgetti, L. Bartolini, M. Cecchi, H. Timmerman, R. Leurs, G. Pepu, M. G. Giovannini, *Br. J. Pharmacol.* **1996**, *119*, 1656–1664; K. Onodera, S. Miyazaki, M. Imaizumi, H. Stark, W. Schunack, *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1998**, *357*, 508–513.

[22] H. Stark, M. Kathmann, E. Schlicker, W. Schunack, B. Schlegel, W. Sippl. *Mini Rev. Curr. Med. Chem*. **2004**, in press; R. Leurs, P. Blandina, C. Tedford, H. Timmerman, *Trends Pharmacol. Sci*. **1998**, *19*, 177-183.

[23] R. E. Brown, D. R. Stevens, H. L. Haas, *Prog. Neurobiol.* **2001**, *63*, 637–672.

[24] C. Maslinski, W. Fogel in *Handbook of Experimental Pharmacology* (Ed.: B. Uvnäs), Springer, Berlin-Heidelberg, **1991**, pp. 165–189.

[25] N. Kitanaka, J. Kitanaka, T. Oue, Y. Tada, T. Tanaka, M. Takemura, *Jpn. J. Pharmacol.* **2002**, *88*, 85-92;L. Wang, B. Thomae, B. Eckloff, E. Wieben, R. Weinshilboum, *Biochem. Pharmacol.* **2002**, *64*, 699–710.

[26] J.-C. Schwartz, H. Pollard, S. Bischoff, M. C. Rehault, M. Verdière-Sahuque, *Eur. J. Pharmacol.* **1971**, *16*, 326–335.

[27] M. A. Beaven in *Pharmacology of Histamine Receptors* (Ed.: C. R. Ganellin, M. E. Parsons), Wright, Bristol, **1982**, 103–145.

[28] W. G. Barnes, L. B. Hough, *J. Neurochem*. **2002**, *82*, 1262–1271; J. R. Horton, K. Sawada, M. Nishibori, X. Zhang, X. Cheng, *Structure* **2001**, *9*, 837–849.

[29] Y. Itoh, R. Oishi, N. Adachi, K. Saeki, *J. Neurochem.* **1992**, *58*, 884–889.

[30] J. Apelt, X. Ligneau, H.-H. Pertz, J.-M. Arrang, C. R. Ganellin, J.-C. Schwartz, W. Schunack, H. Stark, *J. Med. Chem.* **2002**, *45*, 1128–1141.

[31] S. Graßmann, J. Apelt, W. Sippl, X. Ligneau, H. H. Pertz, Y. H. Zhao, J.-M. Arrang, C. R. Ganellin, J.-C. Schwartz, W. Schunack, H. Stark, *Bioorg. Med. Chem.* **2003**, *11*, 2163–2174.

[32] M. Nishibori, R. Oishi, Y. Itoh, K. Saeki, *Jpn. J. Pharmacol.* **1991**, *55*, 539–546.

[33] A. R. Surrey, R. A. Cutler, *J. Am. Chem. Soc.* **1951**, *73*, 2623–2626.

[34] M. Garbarg, J.-M. Arrang, A. Rouleau, X. Ligneau, M. D. Trung Tuong, J.-C. Schwartz, C. R. Ganellin, *J. Pharmacol. Exp. Ther.* **1992**, *263*, 304–310.

[35] X. Ligneau, S. Morisset, J. Tardivel-Lacombe, F. Gbahou, C. R. Ganellin, H. Stark, W. Schunack, J.-C. Schwartz, J.-M. Arrang, *Br. J. Pharmacol*. **2000**, *131*, 1247–1250.

[36] H. Finch, E. A. Peterson, S. A. Ballard, *J. Am. Chem. Soc*. **1952**, *74*, 2016–2018.

[37] J. v. Braun, F. Zobel, *Liebigs Ann. Chem.* **1925**, *445*, 247–266.

[38] G. Meier, J. Apelt, U. Reichert, S. Graßmann, X. Ligneau, S. Elz, F. Leurquin, C.R. Ganellin, J.-C. Schwartz, W. Schunack, H. Stark, *Eur. J. Pharm. Sci.* **2001**, *13*, 249–259.

[39] D. Yang, J. L. Soulier, S. Sicsic, M. Muthe, B. Bremont, *J. Med. Chem.* **1997**, *40*, 608–621.

[40] X. Ligneau, M. Garbarg, M. L. Vizuette, J. Diaz, K. Purand, H. Stark, W. Schunack, J.-C. Schwartz, *J. Pharmacol. Exp. Ther.* **1994**, *271*, 452–459.

[41] Y.-C. Cheng, W. H. Prussoff, *Biochem. Pharmacol.* **1973**, *22*, 3099–3108.

[42] V. P. Whittaker, *Ann. N. Y. Acad. Sci.* **1966**, *137*, 982–998.

[43] R. R. Bowsher, K. M. Verburg, D. P. Henry, *J. Biol. Chem*. **1983**, *258*, 12215–12220.

[44] M. Garbarg, M. D. Trung Tuong, C. Gros, J.-C. Schwartz, *Eur. J. Pharmacol.* **1989**, *164*, 1–11.