Institut für Pharmazie[1], Freie Universität Berlin, Germany; Laboratoire Bioprojet[2], Paris, France; Department of Chemistry[3], Christopher Ingold Laboratories, University College London, U.K.; Unité de Neurobiologie et Pharmacologie Moléculaire (U. 573)[4], Centre Paul Broca de l'INSERM, Paris, France; Institut für Pharmazeutische Chemie[5], Johann Wolfgang Goethe-Universität, Biozentrum/ZAFES, Frankfurt/Main, Germany

Search for histamine H_3 receptor antagonists with combined inhibitory potency at N^{τ}-methyltransferase: ether derivatives

J. Apelt[1], S. Grassmann[1], X. Ligneau[2], H. H. Pertz[1], C. R. Ganellin[3], J.-M. Arrang[4], J.-C. Schwartz[4], W. Schunack[1], H. Stark[5]

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Prof. Dr. Holger Stark, Johann Wolfgang Goethe-Universität, Institut für Pharmazeutische Chemie, Biozentrum/ZAFES, Marie-Curie-Straße 9, 60439 Frankfurt/Main, Germany
h.stark@pharmchem.uni-frankfurt.de

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With the recent development of new hybrid compounds having histamine H_3 receptor antagonist with combined histamine N^{τ}-methyltransferase (HMT) inhibitory potency an innovative approach was described in the research of novel lead compounds modulating histaminergic neurotransmission. Several compounds containing an ether moiety derived from the recently published 4-(3-piperidinopropoxy)phenylaminoquinoline derivatives (like FUB 836), were synthesized in this study and tested for their affinity at cloned human histamine H_3 (hH_3) receptors and on the inhibition of rat HMT. Besides different heterocycles, e.g. nitro- or amino-substituted pyridines, quinolines, benzothiazole or pyrroline, three classes of compounds were produced: heteroaromatic 3-piperidinopropyl ethers, keto- or imino-substituted 4-(3-piperidinopropyl)phenyl ethers and 4-(3-piperidinopropyl)phenyl ethers with substituted (alkyl)aminopyridines. Whereas the (3-piperidinopropoxy)heterocycles showed only moderate activities on both test models, the 4-(3-piperidinopropoxy)phenyl derivatives were identified as potent histamine H_3 receptor ligands and/or HMT inhibitors. K_i values up to 0.42 nM were found for the affinity to the hH_3 receptor. HMT inhibitory potency was identified with IC_{50} values about 0.3 μM for the most potent compounds in this series. Comparison of the pyridine-containing derivatives to recently published quinoline analogues showed a decrease in potencies for the pyridines. The dual activity, H_3 receptor affinity and HMT inhibition, was moderate to good. For all compounds affinities at hH_3 receptors were higher than their inhibitory HMT potencies. The described new histamine H_3 receptor antagonists with an ether moiety represent a further promising step in our investigations for a dual activity.

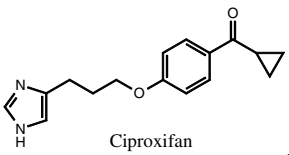
1. Introduction

Histamine is not only known for its allergic response and the gastric acid secretions, but also functions as a neurotransmitter in the peripheral and mainly in the central nervous system (CNS) (Arrang et al. 1983; Schwartz et al. 1991). Synthesized from its precursor L-histidine by cytoplasmatic L-histidine decarboxylase histamine is stored vesicularly (Brown et al. 2001). Histamine accounts for different (patho)physiological processes by interaction with four histamine receptor subtypes named in historical order H_1, H_2, H_3, and H_4 (Hill et al. 1997; Nakamura et al. 2000). The recently cloned histamine H_3 receptor is predominantly located presynaptically in the CNS from where it modulates the synthesis and release of histamine as well as the release of several other monoaminergic and peptidergic neurotransmitters (Arrang et al. 1983, 1985, 1987; Hill et al. 1997; Lovenberg et al. 1999). The histamine H_3 receptor regulates histamine release by a negative feedback mechanism as an autoreceptor. Histamine is inactivated in the CNS mainly by the ubiquitously distributed and recently cloned enzyme histamine N^{τ}-methyltransferase (HMT, E.C. 2.1.1.8) methylating the imidazole ring in the 1-position using *S*-adenosyl-L-methionine (SAM) as methyl donor (Hill et al. 1997; Horton et al. 2001; Kitanaka et al. 2002; Wang et al. 2001). In further steps or in another pathway the aliphatic amino functionality is converted into the corresponding aldehyde by either diaminooxidase (DAO, E.C. 1.4.3.6) (in the periphery) or monoaminooxidase B (MAO-B, E.C. 1.4.3.4) (in the CNS) which is finally transformed into (N^{τ}-methylimidazol-4-yl)acetic acid by special oxidases. Since DAO is absent in the CNS, methylation of histamine appears to be the preferred pathway of central metabolism, whereas in the periphery the oxidative deamination of histamine by DAO also leads to inactivation (Maslinski et al. 1991).

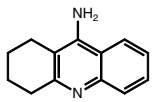
Antagonism/inverse agonism at the histamine H_3 receptor increases brain histamine release by interrupting the nega-

tive feedback mechanism. Obstruction of the metabolism by an inhibition of the histamine methylating enzyme HMT enhances histamine levels in the CNS. An enhancement of histaminergic neurotransmission in the CNS might be useful in neurodegenerative diseases like Morbus Alzheimer (Morisset et al. 1996; Panula et al. 1995), memory and learning deficits (Blandina et al. 1996; Onodera et al. 1998) and attention-deficit hyperactivity disorder (Leurs et al. 1998).

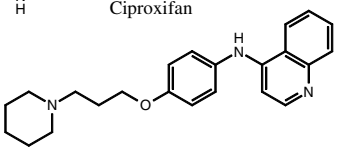
Several compounds are known as potent histamine H_3 receptor antagonists/inverse agonists or as HMT inhibitors. Ciproxifan belongs to the imidazole-containing class of acylated proxifans which are potent antagonists/inverse agonists (Ligneau et al 1998; Ligneau et al. 2000). Replacement of the imidazole moiety led to a new class of histamine H_3 receptor antagonists having a *N*-containing aliphatic heterocycle which is in most cases a piperidino group (Ganellin et al. 1998; Stark 2003). Besides several antimalarials the acetylcholinesterase inhibitor tacrine was identified as a potent HMT inhibitor (Cumming et al. 1992; Nishibori et al. 1991). In the past most compounds failed to have a combined activity: histamine H_3 receptor antagonism and HMT inhibition. Recently we have described a new class of histamine H_3 receptor ligands with these dual activities (Apelt et al. 2002). Whereas FUB 775 was identified as one of the most potent HMT inhibitors known so far with an IC_{50} value of 0.016 μM, it was not a potent histamine H_3 receptor antagonist. The design of FUB 836 led to a highly potent histamine H_3 receptor antagonist with simultaneously high HMT inhibitory potency. This ether showed one of the highest affinities in a binding assay on cloned human histamine H_3 receptors so far with a K_i value of 91 pM. Regarding HMT inhibition FUB 836 belongs to the potent inhibitors showing an IC_{50} value in the nanomolar concentration range ($IC_{50} = 51$ nM), which is two-fold more potent than tacrine.



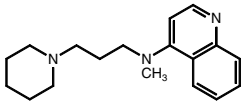
Ciproxifan



Tacrine



FUB 836



FUB 775

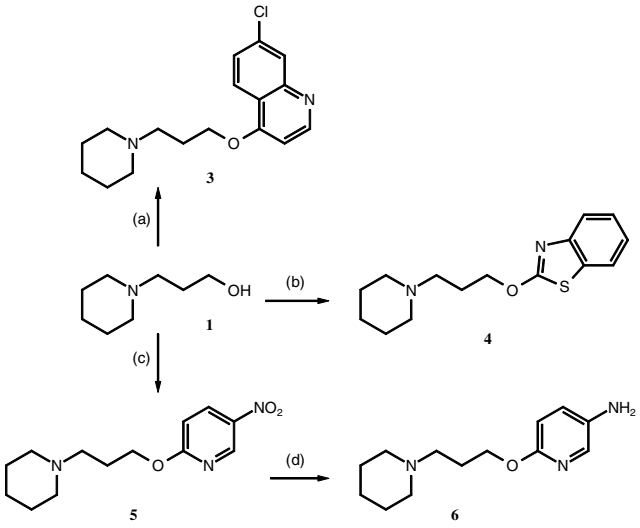
In this study compounds structurally related to FUB 836 were investigated for their *in vitro* affinities at human histamine H_3 receptor and inhibitory potencies on rat HMT. The binding affinities were measured on human H_3 receptors stably expressed in CHO cells. The inhibitory HMT potencies were determined on HMT purified from rat kidney. Besides different heterocyclic moieties the described compounds have in addition to their 3-piperidinopropyl moiety an aromatic ether moiety as a common structural feature.

2. Investigations, results and discussion

2.1 Chemistry

The key intermediate in the series of the heteroaromatic ethers was 3-piperidinopropanol (**1**) (Meier et al. 2001),

Scheme 1

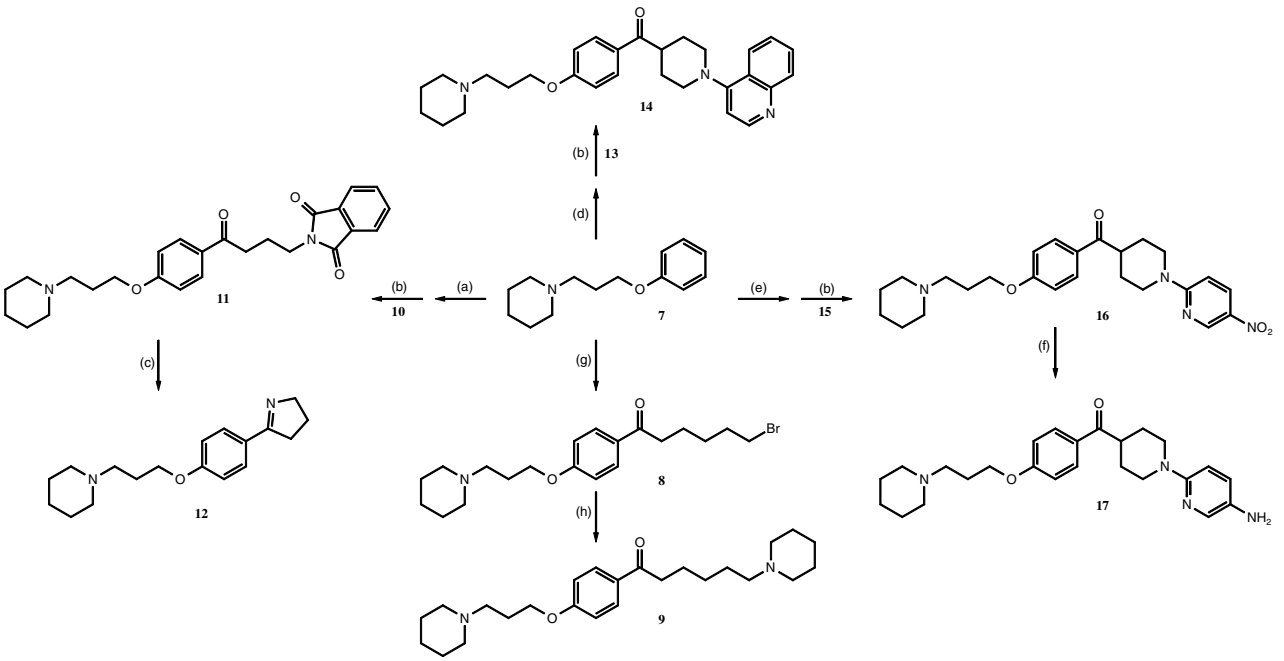


(a) 4,7-Dichloroquinoline, NaH, THF, 60 °C, 12 h; (b) 2-chlorobenzothiazole, NaH, THF, 60 °C, 12 h; (c) 2-chloro-5-nitropyridine, NaH, THF, 60 °C, 12 h; (d) H_2 (1 bar), Pd/C, r.t., 12 h

which was obtained by reaction of piperidine with 3-chloropropanol. After distillation the oily product was coupled with chloro-substituted heterocycles in a Williamson ether synthesis using sodium hydride as a strong base and THF as solvent (Scheme 1) (Clinton et al. 1949). Due to high electronegativity of the ring nitrogen of the heterocycles a nucleophilic substitution was promoted in the *ortho*- and *para*-position depending on the position of the leaving group. Ethers **3**–**5** were isolated as salts of oxalic acid after purification and crystallization. Hydrogenation of the nitropyridine derivatives using palladium on carbon catalyst led to the corresponding aminopyridines (Lappin and Slezak 1950).

The series of keto- or imino-substituted phenylethers (Scheme 2) resulted from reaction of 1-(3-phenoxypropyl)piperidine (**7**) with acyl chlorides by Friedel-Crafts acylation (Mahoto 2000). Piperidine reacted with 3-phenoxypropylbromide in the presence of potassium carbonate to form the second key intermediate **7**. Purification of the oily product was best achieved by crystallizing the salt made by the use of hydrochloric acid. Due to possible side reactions of the piperidine moiety with the activated carboxylic acid this transformation was important for the acylation in the following reaction step. The corresponding carboxylic acids were obtained by different procedures: *N*-3-Carboxypropylphthalimide (**10**) resulted from melting of 4-aminobutyric acid with an excess of potassium phthalic anhydride at 180 °C for a short time (Böttcher 1913). The heterocyclic carboxylic acids **13** and **15** were obtained by reaction of the corresponding chloro-substituted heterocycle with piperidine-4-carboxylic acid in molten phenol at high temperatures. Phenol increased the reactivity of the heterocycle by forming unstable phenolether intermediates with the heterocycles (Surrey and Cuttler 1951). The phenolether is more reactive than the halogen substituted heterocycle since phenoxy is a better leaving group and therefore, the yields increased. The intermediates were purified by crystallization as hydrochloride salts. Friedel-Craft acylation was performed in nitrobenzene with $\mathbf{7} \cdot HCl$, $AlCl_3$ and the carboxylic acid chlorides which were obtained in most cases using thionyl chloride.

Scheme 2

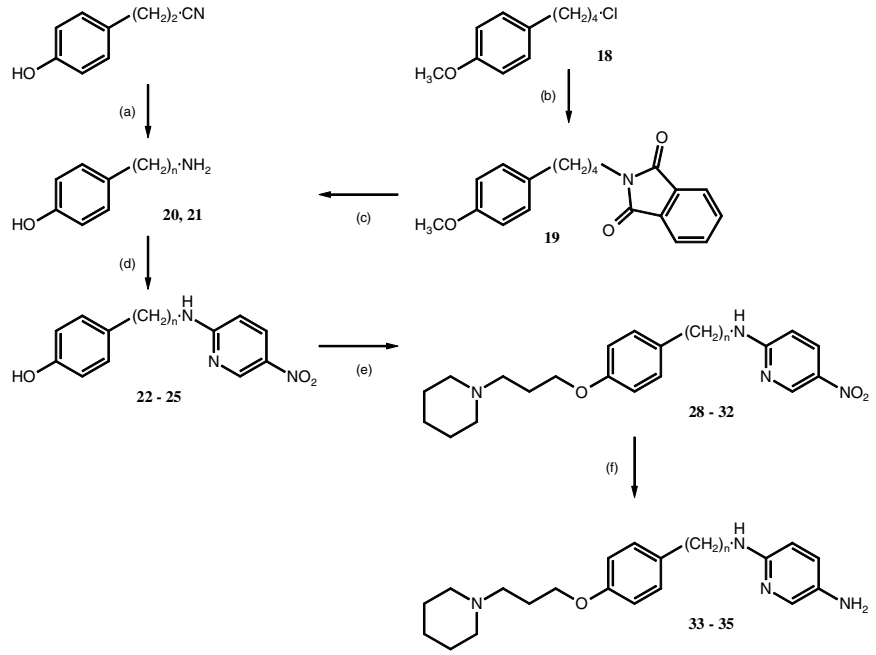


(a) 4-Aminobutyric acid, potassium phthalimide, 180 °C, 0,5 h; (b) *i:* $SOCl_2$, THF, 50 °C, 2 h; *ii:* $AlCl_3$, nitrobenzene, r.t., 3 d; (c) HCl (5 M), reflux, 12 h; (d) piperidine-4-carboxylic acid, 4-chloroquinoline, phenol, 140 °C, 12 h; (e) piperidine-4-carboxylic acid, 2-chloro-5-nitropyridine, phenol, 140 °C, 12 h; (f) H_2 (1 bar), Pd/C, r.t., 12 h; (g) 6-bromohexanoyl chloride, $AlCl_3$, nitrobenzene, r.t., 3 d; (h) piperidine, K_2CO_3, KI, EtOH, reflux, 12 h

The unsymmetrical dipiperidino derivative **9** was obtained by reaction of **8** with an excess of piperidine (analogously to **7**). Refluxing of the phthalimide **11** with hydrochloric acid (5 M) led to cleavage of the protecting group. Instead of obtaining the free primary amine an intramolecular cyclisation process occurred and resulted in the stable cyclic imine **11** under acid catalysis (Gabriel and Colman 1908; Reddelien 1910). After basification **11** was purified by column chromatography. Hydrogenation of the nitro derivative **16** was performed as described before.

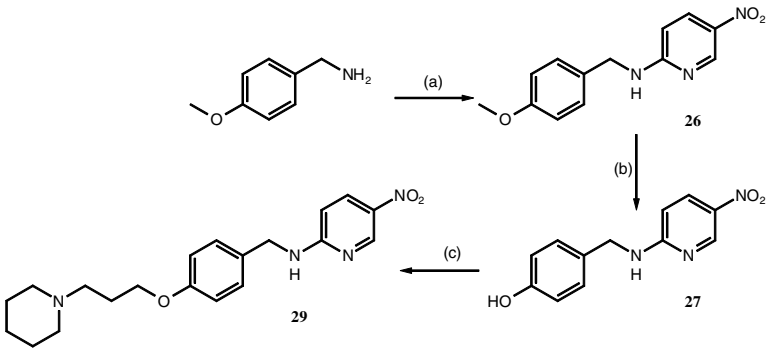
Another key intermediate for this class of histamine H_3 receptor antagonists having a propyloxyphenyl spacer is (3-chloropropyl)piperidine · HCl (**2**), which was obtained by chlorination of 3-piperidinopropanol (**1**) using thionyl chloride. Other important synthons in this series are different 4-(aminoalkyl)phenols (**20**, **21,** and commercially

Scheme 3



(a) $LiAlH_4$, THF, reflux, 2 h; (b) potassium phthalimide, KI, DMF, reflux, 12 h; (c) *i:* BBr_3, CH_2Cl_2, −78 °C, 30 min; *ii:* r.t., 3 h; *iii:* 6 N HCl, reflux, 12 h; (d) 2-chloro-5-nitropyridine *i:* (n = 0) KI, 2 N HCl, EtOH, reflux, 12 h; *ii:* (n = 2–4) phenol, 140 °C, 12 h; (e) 1-(3-chloropropyl)piperidine (**2**), K_2CO_3, KI, DMF, reflux, 12 h; (f) H_2 (1 bar), Pd/C, r.t., 12 h

Scheme 4



(a) 2-Chloro-5-nitropyridine, KI, TEA, EtOH, reflux, 2 h; (b) *i*: BBr_3, CH_2Cl_2, −78 °C, 30 min; *ii*: r.t., 3 h; (c) (3-chloropropyl)piperidine (**2**), K_2CO_3, KI, DMF, reflux, 12 h

available compounds). 4-(3-Aminopropyl)phenol (**20**) was obtained by reduction of the corresponding nitrile with lithium aluminium hydride. 4-(4-Aminobutyl)phenol (**21**) resulted in good overall yield from Gabriel synthesis of chlorinated 4-(4-methoxyphenyl)butanol (**18**) with potassium phthalimide (Gabriel and Weiner 1888), followed by cleavage of the methyl phenyl ether **19** with boron tribromide (McOmie et al. 1968) and finally cleavage of the phthalimide under acidic conditions. The 4-(ω-aminoalkyl)phenols were coupled with 2-chloro-5-nitropyridines by nucleophilic substitution. 4-Hydroxyaniline reacted with the corresponding pyridine derivative with heating in ethanol and addition of a catalytic amount of HCl. Protonation of the ring nitrogen of the halogenated pyridines increased the reactivity of the heterocycle in the 2-position (Maggiolo and Phillips 1951). Pyridine **22** was purified by column chromatography. The reaction of the other 4-hydroxyphenylamines with the pyridines was carried out in molten phenol under reaction conditions mentioned above (analogously to **13**, **15**). The products **23**–**25** were isolated as free bases. In the last step the intermediates obtained were reacted in a Williamson ether synthesis with (3-chloropropyl)piperidine (**2**) to **28**–**32** in an aprotic solvent (Claisen and Eisleb 1913).

The benzylic compound **29** was obtained by a different procedure because of instabilities of the benzylic structures (Scheme 4). 4-Methoxybenzyl amine reacted with 2-chloro-5-nitropyridine in ethanol under mild conditions using triethylamine as proton acceptor to form the heterocyclic benzylic compound **26**. Cleavage of the methyl phenyl ether was carried out with boron tribromide. The resulting *N*-(4-hydroxybenzyl)-2-amino-5-nitropyridine (**27**) was coupled with **2** to **29** (see above).

2.2. Pharmacology

2.2.1. Binding assay at human histamine H_3 receptors

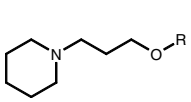
The affinity of the compounds was determined by measuring the displacement of the [^{125}I]iodoproxyfan binding to human histamine H_3 receptors (Ligneau et al. 1994; Ligneau et al. 2000). In the series of the 3-piperidinopropyl heteroaromatic ethers **3**–**6** the compounds showed moderate potencies at human H_3 receptors (100 nM–235 nM) (Table 1). The benzothiazole **4** possesses higher affinity than the quinoline **3** as well as the pyridines **5** and **6**. The amino-substituted compound **6** is about three-fold more potent than its nitro-substituted analogue **5**.

In contrast to these heteroaromatic ethers, in the series of the 4-(3-piperidinopropoxy)phenyl derivatives the potencies clearly increased. The series of the keto- or imino-substituted phenyl ethers was derived from the prototype ciproxifan which is a highly potent histamine H_3 receptor antagonist/inverse agonist (Ligneau et al. 2000). The phenyl ether compounds containing an acylated piperidine spacer showed K_i values from 4.5 to 14 nM (**13**, **16**, **17**). Similar to compounds **5** and **6** the hydrogenated 5-aminopyridine **17** with an increased basicity possessed slightly higher affinity than its nitro analogue **16**. Improvement in affinity was obtained with compounds **9** and **12**. In the class of the keto-substituted 4-(3-piperidinopropoxy)-phenyl derivatives a piperidino-heteroaromatic moiety did not increase affinity (**13**, **16**, **17**). Although the substituted pyridine moiety could maintain affinity the length and the orientation of the spacer had important influence on affinity. The nitro-substituted aminopyridine **28** without an alkyl spacer between phenyl and aminopyridine showed low nanomolar affinity. Insertion of an alkyl spacer from one to four methylene groups between phenyl and pyridinylamine (**29**–**32**) slightly decreased the affinity. The diaminopyridine derivative **35** with a four methylene group spacer was more potent than its nitro-substituted analogue **32** whereas the opposite is true for the related compounds with a three methylene spacer (**31** vs. **34**). However, in this series of nitropyridines a short or a missing alkyl spacer and a nitro moiety seem to be advantageous.

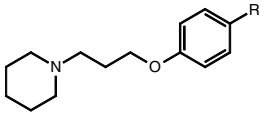
2.2.2. In vitro screening for HMT inhibitory activity

The compounds were screened for their ability to inhibit the metabolism of histamine. Inhibition was measured by determination of blocking the formation of the metabolite N^{τ}-methylhistamine (Apelt et al. 2002). As reference compounds tacrine and FUB 836 were used inhibiting the enzyme with IC_{50} values of 0.11 μM and 0.051 μM, respectively (Apelt et al. 2002). In the series of the (3-piperidinopropyl)heteroaromatic ethers moderate to good inhibitory potencies were found (Table 1). Since all compounds showed respectable potencies despite the structure of the substituents one may presume that the (3-piperidinopropyloxy)aryl group could be responsible for some HMT binding. Within the heterocyclic substituted ethers the chloro-substituted quinoline **3** was more potent than the benzothiazole **4** or the pyridines **5** and **6**.

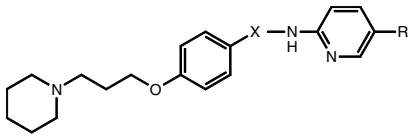
Table 1: Chemical structures and pharmacological screening results of novel piperidine derivatives for human histamine H_3 receptor binding affinity and inhibitory potency on rat histamine *N*-methyltransferase



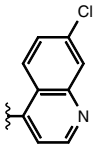
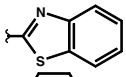
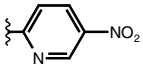
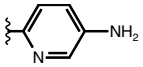
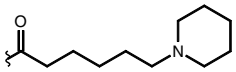
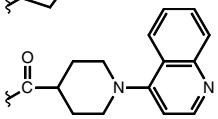
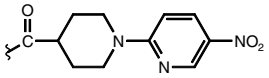
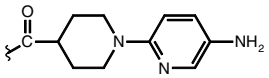
S1



S2



S3

Compd.	Structure (S1, S2, or S3)	X	R	H_3 K_i (nM)[a]	HMT Inhibition $IC_{50} \pm SEM(\mu M)$[b]
3	S1			235	2.6 ± 0.5
4	S1			96[c]	21 ± 1
5	S1			82	34 ± 7
6	S1			258	53 ± 11
9	S2			0.42	8.9 ± 1.4
12	S2			0.60	9.0 ± 1.2
13	S2			14	0.31 ± 0.04
16	S2			5.8	1.5 ± 0.1
17	S2			4.5	2.0 ± 0.2
28	S3	–	NO_2	1.0	3.8 ± 0.1
29	S3	CH_2	NO_2	2.8	4.2 ± 0.1
30	S3	$(CH_2)_2$	NO_2	2.6	2.8 ± 0.1
31	S3	$(CH_2)_3$	NO_2	2.7	1.7 ± 0.2
32	S3	$(CH_2)_4$	NO_2	14	1.7 ± 0.1
33	S3	$(CH_2)_2$	NH_2	4.7	0.31 ± 0.07
34	S3	$(CH_2)_3$	NH_2	9.5	1.3 ± 0.2
35	S3	$(CH_2)_4$	NH_2	7.0	0.34 ± 0.01
Ciproxifan[d,e]				9.0	46
FUB 836[e]				0.051	0.091
Tacrine[e]				0.11	n.d.[f]

[a] [^{125}I]Iodoproxyfan binding assay at human H_3 receptors stably expressed in CHO cells. [b] HMT assay on isolated enzyme from rat kidney (mean value with standard error of the mean (SEM). [c] Functional histamine release assay using rat cerebral cortex (Ligneau et al. 1994). [d] Data from Ligneau et al. (2000). [e] Data from Apelt er al. (2002). [f] n.d., not determined

With the series of phenyl ether derivatives the potencies mainly increased in comparison to that of the heteroaromatic ethers. In the series of phenyl ethers the aminonitropyridines **16** and **28**–**32** showed inhibitory potencies in the range from 1.5 to 4.2 μM and the (di)aminopyridines (**17**, **33**–**35**, and under broad structural view also **13**) from 0.31 to 2.0 μM. The pyridine derivatives **16**, **17**, **28**–**32**, and **34** inhibit the enzyme with IC_{50} values in the low micromolar concentration range and the aminoquinoline **13** and the diaminopyridines **33** and **35** even showed submicromolar affinities. In comparison to related quinoline-substituted analogues (e.g., FUB 836) the current pyridines and quinolines did not reach the HMT inhibitory activity of the novel reference compounds.

2.2.3. Combined histamine H_3 receptor affinity and HMT inhibition

Recently it was shown that both activities, histamine H_3 receptor affinity and HMT inhibitory potency, can be combined in one hybrid molecule. FUB 836 is a prototype for this dual activity as one of the most potent HMT inhibitors ($IC_{50} = 0.051$ μM) and a compound with one of the highest histamine H_3 receptor affinity ($K_i = 0.091$ nM) known so far (Apelt et al. 2002). The newly presented compounds also showed combined activity in a nanomolar concentration range for H_3 and (sub)micromolar concentration range for HMT. Whereas the heteroaromatic ethers have moderate activity, the 4-(3-piperidinopropoxy)phenyl

derivatives demonstrate high potency for both activities, but much lower than the reference compound FUB 836. In contrast to FUB 836, in these series activities could not be combined in one compound with similar potencies at the two targets. Some compounds have a relatively high HMT inhibitory potency (**13**, **33**, **35**) and others represent potent histamine H_3 receptor ligands (**9**, **12**, **28**).

2.3. Conclusion

Derived from the recently published FUB 836, several compounds with an ether moiety and a heterocycle were investigated for their histamine H_3 receptor affinities and their HMT inhibitory potencies. In contrast to the quinoline-containing potent histamine H_3 receptor antagonists with combined HMT inhibition, the described compounds only showed moderate to good potencies. Whereas some compounds were identified as potent HMT inhibitors, they only present moderate histamine H_3 receptor affinity and *vice versa*. A pyridine moiety did not seem to be advantageous for these combined activities at a low concentration activity level. In the class of the 4-(3-piperidinopropoxy)phenyl(alkyl) derivatives nitro-substituted pyridines possessed improved histamine H_3 receptor affinity, whereas some of the hydrogenated, amino-substituted analogues were potent HMT inhibitors, possibly due to an increased basicity. In comparison to the analogues (like FUB 836) with a quinoline moiety instead of a pyridine, the pyridines are less potent. Despite the decrease in activity, the ethers present a promising new lead for histamine H_3 receptor ligands with combined HMT inhibitory potency. Possibly due to a second basic centre in the molecule both activities could be affected. Further investigations should be performed describing the role of the heterocycle and the additional basic centre. In addition to the results obtained in this investigation one may suggest that having an additional basic moiety in the development of other leads may also provide inhibitory HMT activity.

3. Experimental

3.1. Chemistry

3.1.1. General procedures

Melting points were measured on an Electrothermal IA 9000 digital apparatus (Büchi) and are uncorrected. ^{1}H NMR spectra were recorded on an Advance DPX 400 spectrometer (Bruker 400). Chemical shifts are expressed in ppm downfield from internal Me_4Si 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. 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, Me_2SO as solvent, glycerol as matrix). Elemental analyses (C, H, N) were determined on Perkin Elmer 240 B or 240 C and were within ± 0.4% of the theoretical values. Column chromatography was carried out using silica gel 40–63 µm. Thin layer chromatography was performed on silica gel F_{254} plates (Merck). All final compounds were crystallized and recrystallized as salts of oxalic acid or hydrochloric acid from ethanol/diethyl ether unless otherwise indicated. The following abbreviations are used: BenzThiaz, benzothiazole; CF_3COOD, trifluoroacetic acid-d; DMF, *N*,*N*-dimethylformamide; DMSO, dimethylsulfoxide; Et_2O, diethyl ether; EtOAc, ethyl acetate; EtOH, ethanol; MeOH, methanol; Ph, phenyl; Quin, quinolinyl; r.t., room temperature; TEA, triethyl amine; THF, tetrahydrofuran.

3.1.2. Synthesis and analytics

3.1.2.1. 3-Piperidinopropanol (**1**) (Meier et al. 2001)

3-Chloropropanol (4.72 g, 50 mmol), piperidine (8.5 g, 100 mL), and a catalytic amount of KI were refluxed in 100 mL acetone for 12 h. The solvent was evaporated and the product was obtained through distillation. Yield: 85%; ^{1}H NMR (CF_3COOD) δ 7.16 (br, 1 H, OH), 4.07 (t, J = 5.7 Hz, 2 H, C*H*$_2$OH), 3.79 (m, 2 H, Pip-2-H$_{äq}$, Pip-6-H$_{äq}$), 3.43 (t, J = 7.1 Hz, 2 H, PipCH$_2$), 3.00 (m, 2 H, Pip-2-H$_{ax}$, Pip-6-H$_{ax}$), 2.24 (m, 2 H, PipCH$_2$C*H*$_2$), 1.89–2.13 (m, 5 H, 2Pip-3-H, Pip-4-H$_{äq}$, 2Pip-5-H), 1.64 (m, 1 H, Pip-4-H$_{ax}$); MS (70 eV), m/z (%) 143 ([M^+], 8).

3.1.2.2. 3-Piperidinopropylchloride hydrochloride **(2)** (Meier et al. 2001)

To a solution of **1** (6.1 g, 50 mmol) in 20 mL THF was added $SOCl_2$ (6.5 g, 55 mmol) under cooling with water. The mixture was stirred for 2 h at 50 °C. After removing the excess of $SOCl_2$ the residue was crystallized in EtOH/Et_2O. Yield: 97%; ^{1}H NMR ([D_6]DMSO) δ 10.53* (s, 1 H, NH^+), 3.73 (t, J = 6.4 Hz, 2 H, CH_2Cl), 3.38–3.41 (m, 2 H, Pip-2-H$_{äq}$, Pip-6-H$_{äq}$), 3.06–3.10 (m, 2 H, PipCH$_2$), 2.80–2.89 (m, 2 H, Pip-2-H$_{ax}$, Pip-6-H$_{ax}$), 2.19 (m, 2 H, C*H*$_2$CH$_2$Cl), 2.16–2.23 (m, 5 H, 2Pip-3-H, Pip-4-H$_{äq}$, 2Pip-5-H), 1.75–1.81 (m, 1 H, Pip-4-H$_{ax}$); MS (70 eV), m/z (%) 161 ([M^+], 3).

3.1.2.3. General procedure for ethers (**3**–**5**)

A suspension of sodium hydride (60% in paraffin oil, 0.08 g, 3 mmol) and 3-piperidinopropanol (**1**) (0.36 g, 2.5 mmol) in 30 mL of dry THF was stirred for 1 h at 60 °C. After adding the chloro-substituted heterocycle the solution was refluxed for 12 h. The solvent was evaporated and the residue was dissolved in ethyl acetate. After washing with potassium carbonate the solvent was evaporated and the residue purified by silica gel chromatography.

3.1.2.3.1. 4-(3-Piperidinopropoxy)-7-chloroquinoline hydrogen oxalate **(3)**

From **1** and 4,7-dichloroquinoline (0.5 g, 2.5 mmol); [Eluent, ethyl acetate/ TEA/ (95 : 5)]. Yield: 79%; ^{1}H NMR ([D_6]DMSO) δ 8.74 (d, J = 5.3 Hz, 1 H, Quin-2-H), 8.15 (d, J = 8.9, 1 H, Quin-5-H), 7.98 (s, 1 H, Quin-8-H),

Table 2: Physical properties of piperidine derivatives

Compd.	Formula	Mw[a] (g/mol)	m.p. (°C)
3	$C_{17}H_{21}ClN_2O \times C_2H_2O_4 \times 1.25\ H_2O$	417.4	179
4	$C_{15}H_{20}N_2OS \times C_2H_2O_4$	366.4	178
5	$C_{13}H_{19}N_3O_3 \times C_2H_2O_4$	355.3	160–161
6	$C_{13}H_{21}N_3O \times 2\ C_2H_2O_4$	415.4	79–80
9	$C_{25}H_{40}N_2O_2 \times 2\ C_2H_2O_4$	580.7	149
12	$C_{18}H_{26}N_2O$	286.4	55
13	$C_{29}H_{35}N_3O_2 \times 2\ C_2H_2O_4$	637.7	200
16	$C_{25}H_{32}N_4O_4 \times 1.5\ C_2H_2O_4$	587.6	186
17	$C_{25}H_{34}N_4O_2 \times 2.5\ C_2H_2O_4$	647.7	173–174
28	$C_{19}H_{24}N_4O_3 \times 2\ C_2H_2O_4$	536.5	199
29	$C_{20}H_{26}N_4O_3 \times C_2H_2O_4$	460.5	149
30	$C_{21}H_{28}N_4O_3 \times 2\ C_2H_2O_4$	564.5	140–141
31	$C_{22}H_{30}N_4O_3 \times C_2H_2O_4$	488.5	90–91
32	$C_{23}H_{32}N_4O_3 \times C_2H_2O_4$	502.6	127–128
33	$C_{21}H_{30}N_4O \times 2\ C_2H_2O_4 \times 0.25\ H_20$	539.1	102–103
34	$C_{22}H_{32}N_4O \times 3\ C_2H_2O_4 \times 0.25\ H_2O$	643.1	82–88
35	$C_{23}H_{34}N_4O \times 3\ C_2H_2O_4$	652.7	94–97

[a] Mw: molecular weight

7.59 (d, J = 9.0 Hz, 1 H, Quin-6-H), 7.05 (d, J = 5.3 Hz, 1 H, Quin-3-H), 4.29 (t, J = 6.3 Hz, 2 H, CH_2OQuin), 2.51 (m, 6 H, 2Pip-2-H, 2Pip-6-H, PipCH$_2$), 2.00 (m, 2H, PipCH$_2$CH_2), 1.49 (m, 4 H, 2Pip-3-H, 2Pip-5-H), 1.39 (m, 2 H, 2Pip-4-H); EI-MS (70 eV), m/z (%) 304 ([M$^+$], 4).

3.1.2.3.2. 2-(3-Piperidinopropoxy)benzothiazole hydrogen oxalate (**4**)

From **1** and 2-chlorobenzothiazole (0.43 g, 2.5 mmol); [Eluent, methylene chloride/methanol (95 : 5, ammonia atmosphere)]. Yield: 55%; ^{1}H NMR (CF$_3$COOD) δ 7.98 (d, J = 8.2 Hz, 1 H, BenzThiaz-4-H), 7.87 (dd, $J_{4\text{-H/5-H}}$ = 8.2 Hz, $J_{5\text{-H/6-H}}$ = 7.4 Hz, 1 H, BenzThiaz-5-H), 7.83 (d, J = 8.0 Hz, 1 H, BenzThiaz-7-H), 7.73 (dd, $J_{5\text{-H/6-H}}$ = 7.5 Hz, $J_{6\text{-H/7-H}}$ = 8.0 Hz, 1 H, BenzThiaz-6-H), 4.94 (t, J = 5.4 Hz, 2 H, CH_2O), 3.80 (m, 2 H, Pip-2-H$_{äq}$, Pip-6-H$_{äq}$), 3.56 (t, J = 5.5 Hz, 2 H, PipCH$_2$), 3.10 (m, 2 H, Pip-2-H$_{ax}$, Pip-6-H$_{ax}$), 2.70 (m, 2 H, PipCH$_2$CH_2), 1.91–2.05 (m, 5 H, 2Pip-3-H, Pip-4-H$_{äq}$, 2Pip-5-H), 1.63–1.66 (m, 1 H, Pip-4-H$_{ax}$); EI-MS (70 eV), m/z (%) 276 ([M$^+$], < 1).

3.1.2.3.3. 5-Nitro-2-(3-piperidinopropoxy)pyridine hydrogen oxalate (**5**)

From **1** and 2-chloro-5-nitropyridine (0.4 g, 2.5 mmol); [Eluent, ethyl acetate/TEA/petroleum ether (95 : 5 : 100)]. Yield: 50%; ^{1}H NMR (CF$_3$COOD) δ 9.39 (s, 1 H, Py-6-H), 9.25 (d, J = 9.6 Hz, 1 H, Py-4-H), 7.75 (d, J = 9.6 Hz, 1 H, Py-3-H), 4.83 (t, J = 5.2 Hz, 2 H, CH_2OPy), 3.80 (m, 2 H, Pip-2-H$_{äq}$, Pip-6-H$_{äq}$), 3.52 (m, 2 H, PipCH$_2$), 3.10 (m, 2 H, Pip-2-H$_{ax}$, Pip-6-H$_{ax}$), 2.60 (m, 2 H, PipCH$_2$CH_2), 1.90–2.17 (m, 5 H, 2Pip-3-H, Pip-4-H$_{äq}$, 2Pip-5-H), 1.64 (m, 1 H, Pip-4-H$_{ax}$); EI-MS (70 eV), m/z (%) 265 ([M$^+$], 3).

3.1.2.4. 5-Amino-2-(3-piperidinopropoxy)pyridine dihydrogen oxalate (**6**)

A solution of **5** (0.27 g, 1 mmol) in 20 mL THF and 50 mg Pd/C (10%) was hydrogenated (1 bar) for 12 h. After filtering and evaporating of the solvent, the residue was purified by silica gel chromatography using ethyl acetate/TEA/methanol (95 : 5 : 5). Yield: 48%; ^{1}H NMR (CF$_3$COOD) δ 9.16 (s, 1 H, Py-6-H), 8.80 (d, J = 9.6 Hz, 1 H, Py-4-H), 7.63 (d, J = 9.6 Hz, 1 H, Py-3-H), 7.81 (br, 1 H, NH), 4.70 (t, J = 6.2 Hz, 2 H, CH_2O), 3.81 (m, 2 H, Pip-2-H$_{äq}$, Pip-6-H$_{äq}$), 3.51 (m, 2 H, PipCH$_2$), 3.10 (m, 2 H, Pip-2-H$_{ax}$, Pip-6-H$_{ax}$), 2.57 (m, 2 H, PipCH$_2$CH_2), 1.90–2.16 (m, 5 H, 2Pip-3-H, Pip-4-H$_{äq}$, 2Pip-5-H), 1.66 (m, 1 H, Pip-4-H$_{ax}$); EI-MS (70 eV), m/z (%) 235 ([M$^+$], 5).

3.1.2.5. 1-(3-Phenoxypropyl)piperidine (**7**)

3-Phenoxypropylbromide (3.23 g, 15 mmol), piperidine (3 mL, 30 mmol), potassium carbonate (6.21 g, 45 mmol) and a catalytic amount of KI were refluxed in 20 mL of ethanol for 12 h. The solvent was evaporated, the residue dissolved in ethyl acetate/water. After washing the organic solvent with potassium carbonate, the product was extracted with hydrochloric acid (2 M). The acid solution was basified and the product was extracted with methylene chloride. A yellow residue resulted after evaporation of the solvent. Yield: 90%; ^{1}H NMR ([D$_6$]DMSO) δ 7.26 (dd, J = 7.8–8.2 Hz, 2 H, Ph-2-H, Ph-6-H), 6.90 (m, 3 H, Ph-3-H, Ph-4-H, Ph-5-H), 3.96 (t, J = 6.4 Hz, 2 H, CH_2O), 2.31–2.38 (m, 6 H, 2Pip-2-H, 2Pip-6-H, PipCH$_2$), 1.84 (m, 2H, PipCH$_2$CH_2), 1.36–1.50 (m, 6 H, 2Pip-3-H, 2Pip-4-H, 2Pip-5-H); EI-MS (70 eV), m/z (%) 219 ([M$^+$], 6).

3.1.2.6. 6-Bromo-1-(4-[3-piperidinopropoxy]phenyl)hexan-1-one (**8**)

Aluminium chloride (6 g, 45 mmol) was added to a solution of 6-bromohexanoyl chloride (3.2 g, 15 mmol) in 15 mL of nitrobenzene. The solution was stirred for 3 d at room temperature after adding **7** · HCl (2.56 g, 10 mmol). After addition of 50 mL of toluene the crude product was extracted with hydrochloric acid (5 M). The acid solution was basified and the product was extracted with methylene chloride. The organic layer was dried with sodium sulfate and evaporated under reduced pressure. Yield: 95%; ^{1}H NMR ([D$_6$]DMSO) δ 7.94 (d, J = 8.9 Hz, 2 H, Ph-3-H, Ph-5-H), 7.02 (d, J = 8.9 Hz, 2 H, Ph-2-H, Ph-6-H), 4.08 (t, J = 6.4 Hz, 2 H, CH_2O), 3.53 (t, J = 6.7 Hz, 2 H, CH_2Br), 2.95 (t, J = 7.2 Hz, 2 H, O=CCH$_2$), 2.31–2.38 (m, 6 H, 2Pip-2-H, 2Pip-6-H, PipCH$_2$), 1.81–1.89 (m, 4 H, PipCH$_2$CH_2, CH_2CH$_2$Br), 1.62 (m, 2 H, O=CCH$_2$CH_2), 1.36–1.51 (m, 8 H, 2Pip-3-H, 2Pip-4-H, 2Pip-5-H, CH_2(CH$_2$)$_2$Br); EI-MS (70 eV), m/z (%) 395 ([M$^+$], 2).

3.1.2.7. 6-Piperidino-1-(4-[3-piperidinopropoxy]phenyl)hexan-1-one dihydrogen oxalate (**9**)

Compound **8** (1 g, 2.5 mmol), piperidine (0,38 mL, 5 mmol), potassium carbonate (1 g, 7,5 mmol) and a catalytic amount of KI were refluxed in 20 mL of ethanol for 12 h. The solvent was evaporated, the residue dissolved in ethyl acetate/water. After washing the organic solvent with potassium carbonate, the organic solvent was evaporated. The residue was purified by silica gel column chromatography using ethyl acetate/TEA (95 : 5). Yield: 47%; ^{1}H NMR (CF$_3$COOD) δ 8.10 (d, J = 8.8 Hz, 2 H, Ph-3-H, Ph-5-H), 7.05 (d, J = 8.8 Hz, 2 H, Ph-2-H, Ph-6-H), 6.77 (br, 1H, NH), 4.37 (t, J = 5.2 Hz, 2 H, CH_2O), 3.87 (m, 2H, Pip-2-H$_{äq}$, Pip-6-H$_{äq}$), 3.73 (m, 2 H, Pip′-2-H$_{äq}$, Pip′-6-H$_{äq}$), 3.53 (t, J = 6.0 Hz, 2 H, PipCH$_2$), 3.25 (t, J = 4.9–5.1 Hz, 2H, Pip'CH$_2$), 3.18 (t, J = 7.1 Hz, 2 H, O=CCH$_2$), 2.97–3.10 (m, 4 H, Pip-2-H$_{äq}$, Pip-6-H$_{äq}$, Pip′-2-H$_{äq}$, Pip′-6-H$_{äq}$), 2.44 (m, 2 H, PipCH$_2$CH_2), 1.88–2.19 (m, 14 H, 2Pip-3-H, Pip-4-H$_{äq}$, 2Pip-5-H, 2Pip′-3-H, Pip′-4-H$_{äq}$, 2Pip′-5-H, O=CCH$_2$CH_2CH$_2$CH_2), 1.54–1.67 (m, 4 H, Pip-4-H$_{ax}$, Pip′-4-H$_{ax}$, O=C(CH$_2$)$_2$CH_2); EI-MS (70 eV), m/z (%) 400 ([M$^+$], 4).

3.1.2.8. *N*-3-Carboxypropylphthalimide (**10**) (Ried and Marquard 1961)

3.1 g (30 mmol) 4-Aminobutyric acid and 8.88 g (60 mmol) of potassium phthalic anhydride were melted at 180 °C for 0.5 h. After adding 30 mL of water the suspension was stirred. The residue was filtered and washed with water and methylene chloride. The organic layers were unified and evaporated. Yield: 96%; ^{1}H NMR ([D$_6$]DMSO) δ 12.06 (s, 1 H, COOH), 7.81–7.88 (m, 4 H, 4Phth-H), 3.61 (t, J = 6.8 Hz, 2 H, CH_2Phth), 2.27 (t, J = 7.2 Hz, 2 H, HOOCCH_2), 1.82 (dt, J = 7.0 Hz, 2 H, HOOCCH$_2$CH_2); EI-MS (70 eV), m/z (%) 233 ([M$^+$], < 1).

3.1.2.9. 4-Phthalimido-1-(4-[3-piperidinopropoxy]phenyl)butan-1-one (**11**)

To a solution of **10** (2.33 g, 10 mmol) in 20 mL THF was added $SOCl_2$ (0.96 mL, 15 mmol) under cooling with water. The mixture was stirred for 2 h at 50 °C. After removing the excess of $SOCl_2$ the residue was dissolved in 10 mL of nitrobenzene, aluminium chloride (4 g, 30 mmol) and **7** · HCl (0.93 g, 3.65 mmol) were added. The mixture was stirred for 3 d at RT. After addition of 50 mL of toluene the crude product was extracted with hydrochloric acid (5 M). The acid solution was extracted with methylene chloride. The organic layer was evaporated and the residue purified by silica gel chromatography using ethyl acetate/TEA/petroleum ether (95 : 5 : 100). Yield: 93%; ^{1}H NMR ([D$_6$]DMSO) δ 7.84 (m, 6 H, 4Phth-H, Ph-3-H, Ph-5-H), 7.02 (d, J = 8.8 Hz, 2 H, Ph-2-H, Ph-6-H), 4.15 (t, J = 6.0 Hz, 2 H, CH_2O), 3.66 (t, J = 6.8 Hz, 2 H, CH_2Phth), 3.46 (m, 2 H, Pip-2-H$_{äq}$, Pip-6-H$_{äq}$), 3.16 (m, 2 H, PipCH$_2$), 3.04 (t, J = 6.9 Hz, 2 H, O=CCH$_2$), 2.87 (m, 2 H, Pip-2-H$_{ax}$, Pip-6-H$_{ax}$), 2.19 (m, 2 H, PipCH$_2$CH_2), 1.94 (m, 2 H, CH_2CH$_2$Phth), 1.69–1.84 (m, 6H, 2Pip-3-H, 2Pip-4-H, 2Pip-5-H); FAB$^+$-MS (Xe, DMSO/m-NO$_2$-Benzylalkohol), m/z (%) 435 ([M + H$^+$], 96).

3.1.2.10. 1-(3-[4-(4,5-Dihydro-3*H*-pyrrolo-2-yl)phenoxy]propyl)piperidine (**12**)

2.18 g (5 mmol) **11** were refluxed with 50 mL of HCl (5 M) for 12 h. The solution was basified and extracted with methylene chloride. The product was purified by silica gel chromatography using ethyl acetate/TEA (95 : 5). Yield: 50%; ^{1}H NMR ([D$_6$]DMSO) δ 7.74 (d, J = 8.7 Hz, 2 H, Ph-2-H, Ph-6-H), 6.96 (d, J = 8.7 Hz, 2 H, Ph-3-H, Ph-5-H), 4.03 (t, J = 6.4 Hz, 2 H, CH_2OPh), 3.89 (t, J = 7.2 Hz, 2 H, Pyr-3-H), 2.86 (t, J = 7.9 Hz, 2 H, Pyr-5-H), 2.31–2.38 (m, 6 H, 2Pip-2-H, 2Pip-6-H, PipCH$_2$), 1.82–1.95 (m, 4 H, PipCH$_2$CH_2, Pyr-4-H), 1.48 (m, 4 H, 2Pip-3-H, 2Pip-5-H), 1.38 (m, 2 H, 2Pip-4-H); EI-MS (70 eV), m/z (%) 286 ([M$^+$], 4).

3.1.2.11. 1-Quinolin-4-yl-piperidin-4-carboxylic acid (**13**)

Piperidine-4-carboxylic acid (0.97 g, 7.5 mmol) and 4-chloroquinoline (0.41 g, 2.5 mmol) were heated in 3 g of phenol for 12 h at 140 °C. After cooling the residue was washed with water and crystallized with isopropanol/HCl in diethyl ether. Yield: 61%; ^{1}H NMR (CF$_3$COOD) δ 8.37 (d, J = 10.3 Hz, 1 H, Quin-2-H), 8.20 (d, J = 8.6 Hz, 1 H, Quin-8-H), 8.01 (m, 1 H, Quin-7-H), 7.96 (d, J = 8.6 Hz, 1 H, Quin-5-H), 7.78 (m, 1 H, Quin-6-H), 7.12 (d, J = 10.8 Hz, 1 H, Quin-3-H), 4.34 (m, 2 H, Pip-2-H$_{äq}$, Pip-6-H$_{äq}$), 3.70 (m, 2 H, Pip-2-H$_{ax}$, Pip-6-H$_{ax}$), 3.05 (m, 1 H, Pip-4-H), 2.19–2.48 (m, 4 H, 2Pip-3-H, 2Pip-5-H); EI-MS (70 eV), m/z (%) 256 ([M$^+$], 100).

3.1.2.12. (4-[3-Piperidinopropoxy]phenyl)-(1-[quinolin-4-yl]piperidin-4-yl)-methanone dihydrogen oxalate (**14**)

Synthesis was performed analogously to the preparation of **11** using **13** (0.39 g, 1.5 mmol); [Eluent, ethyl acetate/TEA (95 : 5)]. Yield: 67%; ^{1}H NMR (CF$_3$COOD) δ 8.35 (d, J = 6.5 Hz, 1 H, Quin-2-H), 8.23 (d, J = 8.6 Hz, 1 H, Quin-8-H), 8.15 (d, J = 7.9 Hz, 2H, Ph-3-H, Ph-5-H), 8.01 (m, 1 H, Quin-7-H), 7.93 (d, J = 8.5 Hz, 1 H, Quin-5-H), 7.77 (m, 1 H, Quin-6-H), 7.12 (m, 3 H, Ph-2-H, Ph-6-H, Quin-3-H), 4.45 (t, J = 7.0 Hz, 2 H, CH_2O), 4.38 (m, 2 H, QuinPip-2-H$_{äq}$, QuinPip-6-H$_{äq}$), 4.03 (m, 1 H, QuinPip-4-H), 3.88 (m, 2 H, Pip-2-H$_{äq}$, Pip-6-H$_{äq}$), 3.78 (m, 2 H, QuinPip-2-H$_{ax}$, QuinPip-6-H$_{ax}$), 3.55 (m, 2 H, PipCH$_2$), 3.07 (m, 2 H, Pip-2-H$_{ax}$, Pip-6-H$_{ax}$), 2.47 (m, 2 H, PipCH$_2$CH_2), 2.30 (m, 4H, 2QuinPip-3-H, 2QuinPip-5-H), 1.91–2.20 (m, 5 H, 2Pip-3-H, Pip-4-H$_{äq}$, 2Pip-5-H), 1.69 (m, 1 H, Pip-4-H$_{ax}$); EI-MS (70 eV), m/z (%) 457 ([M$^+$], 25).

3.1.2.13. 1-(5-Nitropyridin-2-yl)piperidin-4-carboxylic acid (**15**)

Synthesis was performed analogously to the preparation to **13** using 2-chloro-5-nitropyridine (0.4 g, 2.5 mmol). Yield: 75%; ^{1}H NMR (CF$_3$COOD) δ 8.98 (s, 1 H, Py-6-H), 8.68 (d, J = 5.7 Hz, 1 H, Py-4-H), 7.43 (d, J = 5.5 Hz, 1 H, Py-3-H), 4.34 (m, 2 H, Pip-2-H$_{äq}$, Pip-6-H$_{äq}$), 3.76 (m, 2 H, Pip-2-H$_{ax}$, Pip-6-H$_{ax}$), 3.07 (m, 1 H, Pip-4-H), 2.13–2.48 (m, 4 H, 2Pip-3-H, 2Pip-5-H); EI-MS (70 eV), m/z (%) 251 ([M$^+$], 70).

3.1.2.14. (4-[3-Piperidinopropoxy]phenyl)-(1-[5-nitropyridin-2-yl]piperidin-4-yl)methanone hydrogen oxalate (**16**)

Synthesis was performed analogously to the preparation to **11** using **15** (2.88 g, 10 mmol). After addition of 50 mL of toluene the crude product was extracted with hydrochloric acid (5 M). The acid solution was basified and the product was extracted with methylene chloride. The organic layer was evaporated and the residue purified by silica gel chromatography using ethyl acetate/TEA/petroleum ether (95 : 5 : 100). Yield: 81%; ^{1}H-NMR (CF_3COOD) δ 8.96 (s, 1 H, Py-6-H), 8.66 (d, J = 10.2 Hz, 1 H, Py-4-H), 8.11 (d, J = 8.2 Hz, 2 H, Ph-3-H, Ph-5-H), 7.45 (d, J = 10.3 Hz, 1 H, Py-3-H), 7.09 (d, J = 8.2 Hz, 2 H, Ph-2-H, Ph-6-H), 4.37–4.42 (m, 4 H, CH_2O, PyPip-2-H$_{äq}$, PyPip-6-H$_{äq}$), 4.05 (m, 1 H, PyPip-4-H), 3.80–3.89 (m, 4 H, Pip-2-H$_{äq}$, Pip-6-H$_{äq}$, PyPip-2-H$_{ax}$, PyPip-6-H$_{ax}$), 3.54 (m, 2 H, PipCH_2), 3.08 (m, 2 H, Pip-2-H$_{ax}$, Pip-6-H$_{ax}$), 2.46 (m, 2 H, PipCH_2C*H*$_2$), 1.94–2.35 (m, 9 H, 2Pip-3-H, Pip-4-H$_{äq}$, 2Pip-5-H, 2PyPip-3-H, 2PyPip-5-H), 1.68 (m, 1 H, Pip-4-H$_{ax}$); EI-MS (70 eV), m/z (%) 452 ([M$^+$], <1).

3.1.2.15. (4-[3-Piperidinopropoxy]phenyl)-(1-[5-aminopyridin-2-yl]piperidin-4-yl)methanon dihydrogen oxalate (**17**)

A solution of **16** (0.9 g, 2 mmol) in 20 mL THF and 20 mg Pd/C (10%) was hydrogenated (1 bar) for 12 h. After filtering and evaporating of the solvent, the residue was purified by silica gel chromatography using methylene chloride/methanol (96 : 4 ammonia atmosphere). Yield: 82%; ^{1}H NMR (CF_3COOD) δ 8.81 (s, 1 H, Py-6-H), 8.20 (d, J = 10.0 Hz, 1 H, Py-4-H), 8.17 (d, J = 8.9 Hz, 2 H, Ph-3-H, Ph-5-H), 7.42 (d, J = 10.0 Hz, 1H, Py-3-H), 7.09 (d, J = 8.9 Hz, 2 H, Ph-2-H, Ph-6-H), 4.37 (t, J = 5.2 Hz, 2 H, CH_2O), 4.30 (m, 2 H, PyPip-2-H$_{äq}$, PyPip-6-H$_{äq}$), 4.00 (m, 1 H, PyPip-4-H), 3.86–3.90 (m, 2 H, Pip-2-H$_{äq}$, Pip-6-H$_{äq}$), 3.68 (m, 2 H, PyPip-2-H$_{ax}$, PyPip-6-H$_{ax}$), 3.54 (m, 2H, PipCH_2), 3.07 (m, 2 H, Pip-2-H$_{ax}$, Pip-6-H$_{ax}$), 2.46 (m, 2 H, PipCH_2C*H*$_2$), 1.90–2.30 (m, 9 H, 2Pip-3-H, Pip-4-H$_{äq}$, 2Pip-5-H, 2PyPip-3-H, 2PyPip-5-H), 1.68 (m, 1 H, Pip-4-H$_{ax}$); EI-MS (70 eV), m/z (%) 422 ([M$^+$], 27).

3.1.2.16. 4-(4-Methoxyphenyl)butyl chloride (**18**)

To a solution of 4-(4-methoxyphenyl)butanol (5 g, 27.7 mmol) in 20 mL THF was added $SOCl_2$ (2.6 mL, 35 mmol) under cooling with ice. The mixture was stirred at 50 °C for 2 h. THF and $SOCl_2$ were removed under reduced pressure and the residue was dissolved in ethyl acetate. After washing with water the organic layer was removed in vacuum. Yield: 100%; ^{1}H NMR ([D$_6$]DMSO) δ 7.09 (d, J = 8.4 Hz, 2 H, Ph-3-H, Ph-5-H), 6.83 (d, J = 8.5 Hz, 2 H, Ph-2-H, Ph-6-H), 3.71 (s, 3 H, OCH_3), 3.63 (t, J = 6.2 Hz, 2 H, CH_2Cl), 2.50 (t, J = 7.4 Hz, 2 H PhCH$_2$), 1.63–1.70 (m, 4 H, PhCH$_2$(C*H*$_2$)$_2$); MS (70 eV), m/z (%) 198 ([M$^+$], 9).

3.1.2.17. *N*-4-(4-Methoxyphenyl)butyl phthalimide (**19**)

A mixture of **18** (6.1 g, 31 mmol), potassium phthalimide (11.1 g, 60 mmol) and a catalytic amount of KI were refluxed in 50 mL of DMF for 12 h. The solvent was evaporated in vacuum, ethyl acetate was added and the organic layer was washed with 0.1 N K_2CO_3. The ethyl acetate was removed under reduced pressure and resulted in a colourless oil. Yield: 99%; ^{1}H NMR ([D$_6$]DMSO) δ 7.84 (m, 4 H, 4Phth-H), 7.08 (d, J = 8.5 Hz, 2 H, Ph-3-H, Ph-5-H), 6.82 (d, J = 8.5 Hz, 2 H, Ph-2-H, Ph-6-H), 3.71 (s, 3 H, OCH_3), 3.59 (t, J = 6.9 Hz, 2H, CH_2Phth), 2.51 (m, 2 H PhCH$_2$), 1.51–1.61 (m, 4 H, PhCH$_2$(C*H*$_2$)$_2$); MS (70 eV), m/z (%) 309 ([M$^+$], 9).

3.1.2.18. 3-(4-Hydroxyphenyl)propanamine (**20**)

A solution of 3-(4-hydroxyphenyl)propionitrile (4.7 g, 32 mmol) in 10 mL of THF was added dropwise to a suspension of $LiAlH_4$ (1.5 g, 40 mmol) in 20 mL of freshly distilled THF under cooling with ice. The reaction mixture was refluxed for 2 h. The $LiAlH_4$ was decomposed by addition of 2 mL of a saturated solution of potassium sodium tartrate. The solvent was removed in vacuum and the residue was purified by silica gel column chromatography using ethyl acetate/TEA (95 : 5). Yield: 55%; ^{1}H NMR ([D$_6$]DMSO) δ 6.94 (d, J = 8.4 Hz, 2 H, Ph-3-H, Ph-5-H), 6.66 (d, J = 8.4 Hz, 2 H, Ph-2-H, Ph-6-H), 2.44–2.52 (m, 4 H, PhC*H*$_2$CH$_2$C*H*$_2$NH$_2$), 1.57 (m, 2 H, PhCH$_2$C*H*$_2$); MS (70 eV), m/z (%) 151 ([M$^+$], 9).

3.1.2.19. 4-(4-Hydroxyphenyl)butanamine (**21**)

A solution of **19** (9.3 g, 30 mmol) in 50 mL CH_2Cl_2 was cooled to −78 °C and BBr_3 (30 mL, 30 mmol, 1 M solution in CH_2Cl_2) was added. After stirring for 30 min at this temperature the mixture was stirred for 3 h at RT. The BBr_3 was decomposed by addition of 20 mL MeOH. The solvents were removed in vacuum and the residue suspended in water. The suspension was extracted with ethyl acetate. After removal of the solvent under reduced pressure, the residue was refluxed with 30 mL 6 M HCl for 12 h. The sediment was filtered, the aqueous layer evaporated under reduced pressure and the residue was purified by silica column chromatography using CH_2Cl_2/MeOH/NH_3 (9 : 1 : 1). Yield: 65%; ^{1}H NMR ([D$_6$]DMSO) δ 6.95 (d, J = 8.4 Hz, 2 H, Ph-3-H, Ph-5-H), 6.64 (d, J = 8.4 Hz, 2 H, Ph-2-H, Ph-6-H), 2.54 (t, J = 7.0 Hz, 2H, C*H*$_2$NH$_2$), 2.44 (t, J = 7.6 Hz, 2 H, PhC*H*$_2$), 1.51 (m, 2 H, PhCH$_2$C*H*$_2$), 1.33 (m, 2 H, Ph(CH$_2$)$_2$C*H*$_2$); MS (70 eV), m/z (%) 165 ([M$^+$], 17).

3.1.2.20. 4-(5-Nitropyridin-2-yl-amino)phenol (**22**) (Hirauchi and Amano 1979)

4-Hydroxyaniline (1.2 g, 11 mmol), 2-chloro-5-nitropyridine (1.59 g, 10 mmol), a catalytic amount of KI and 1 mL of 2 N HCl were refluxed in 20 mL EtOH for 12 h. The solvent was removed in vacuum and the residue was purified by silica gel column chromatography using ethyl acetate/petroleum ether (3 : 7). Yield: 61%; ^{1}H NMR ([D$_6$]DMSO) δ 9.88* (s, 1 H, NH), 9.32* (s, 1 H, OH), 8.95 (s, 1 H, Py-6-H), 8.20 (d, J = 9.4 Hz 1 H, Py-4-H), 7.40 (d, J = 8.6 Hz, 2 H, Ph-2-H, Ph-6-H) 6.75 (m, 3 H, Py-3-H, Ph-3-H, Ph-5-H). EI-MS m/z (%) 231 (M$^{+\cdot}$, 2).

3.1.2.21. General procedure for phenylalkylaminopyridines (**23**–**25**).

The 2-chloro-5-nitropyridine (1.59 g, 10 mmol) and the phenylalkyl amine (11 mmol) were heated at 140 °C in 3 g phenol for 12 h. After addition of ethyl acetate (20 mL) and 5 M HCl (20 mL) the suspension was stirred for 1 h. After cooling the crude product was purified by silica gel column chromatography using ethyl acetate/petroleum ether (gradient from 1 : 9 to 3 : 7).

3.1.2.21.1. 4-(2-[5-Nitropyridin-2-yl-amino]ethyl)phenol (**23**)

Yield: 45%; ^{1}H NMR ([D$_6$]DMSO) δ 8.91 (s, 1 H, Py-6-H), 8.16 (d, J = 7.7 Hz, 1 H, Py-4-H), 7.14–7.16 (d, J = 8.3 Hz, Ph-2-H, Ph-6-H), 6.68 (d, J = 8.3 Hz, 2 H, Ph-3-H, Ph-5-H), 6.56 (d, J = 9.4 Hz, 1 H, Py-3-H), 3.56 (m, 2 H, C*H*$_2$NH), 2.73 (t, J = 7.5 Hz, 2 H, PhCH$_2$); EI-MS (70 eV), m/z (%) 259 ([M$^+$], 11).

3.1.2.21.2. 4-(3-[5-Nitropyridin-2-yl-amino]propyl)phenol (**24**)

Yield: 62%; ^{1}H NMR ([D$_6$]DMSO) δ 8.90 (s, 1 H, Py-6-H), 8.15 (d, J = 9.6 Hz, 1 H, Py-4-H), 6.98–7.00 (d, J = 8.4 Hz, Ph-2-H, Ph-6-H), 6.66 (d, J = 8.4 Hz, 2 H, Ph-3-H, Ph-5-H), 6.56 (d, J = 9.3 Hz, 1 H, Py-3-H), 3.36 (m, 2 H, C*H*$_2$NH), 2.55 (m, 2 H, PhCH$_2$), 1.80 (m, 2 H, PhCH$_2$C*H*$_2$); EI-MS (70 eV), m/z (%) 273 ([M$^+$], 25).

3.1.2.21.3. 4-(4-[5-Nitropyridin-2-yl-amino]butyl)phenol (**25**)

Yield: 48%; ^{1}H NMR (CF_3COOD) δ 9.02 (s, 1 H, Py-6-H), 8.66 (d, J = 8.1 Hz, 1 H, Py-4-H), 7.49 (d, J = 8.1 Hz, 1 H, Py-3-H), 7.14 (d, J = 8.1 Hz, Ph-2-H, Ph-6-H), 6.92 (d, J = 8.3 Hz, 2 H, Ph-3-H, Ph-5-H), 3.66 (m, 2 H, C*H*$_2$NH), 2.70 (m, 2 H, PhCH$_2$), 1.82–1.90 (m, 4 H, PhCH$_2$(C*H*$_2$)$_2$); EI-MS (70 eV), m/z (%) 287 ([M$^+$], 51).

3.1.2.22. *N*-(4-Methoxybenzyl)-2-amino-3-nitropyridine (**26**)

4-Methoxybenzylamine (1.64 g, 12 mmol), 2-chloro-5-nitropyridine (1.59 g, 10 mmol), 5 mL TEA and a catalytic amount of KI were refluxed in 20 mL ethanol for 12 h. The solvent was evaporated and the residue recrystallized in methanol. Yield: 90%; ^{1}H NMR ([D$_6$]DMSO) δ 8.20 (s, 1 H, Py-6-H), 8.50 (s, 1 H, NH), 8.12 (d, J = 6.9 Hz, 1 H, Py-4-H), 7.25 (d, J = 8.5 Hz, 2 H, Ph-3-H, Ph-5-H), 6.89 (d, J = 8.5 Hz, 2 H, Ph-2-H, Ph-6-H), 6.60 (d, J = 7.5 Hz, 1 H, Py-3-H), 4.54 (m, 2 H, C*H*$_2$NH), 3.73 (s, 3 H, OCH_3); EI-MS (70 eV), m/z (%) 259 ([M$^+$], 14).

3.1.2.23. *N*-(4-Hydroxybenzyl)-2-amino-5-nitropyridine (**27**)

A solution of **26** (1.3 g, 5 mmol) in 20 mL CH_2Cl_2 was cooled to −78 °C and BBr_3 (5 mL, 5 mmol, 1 M solution in CH_2Cl_2) was added. After stirring for 30 min at this temperature the mixture was stirred for 3 h at RT. The BBr_3 was decomposed by addition of 20 mL MeOH. The solvents were removed in vacuum and the residue suspended in water. The suspension was extracted with ethyl acetate. After removal of the solvent under reduced pressure, the residue was purified by silica gel chromatography using ethyl acetate/TEA (95 : 5). Yield: 40%; ^{1}H NMR ([D$_6$]DMSO) δ 8.92 (s, 1 H, Py-6-H), 8.45 (s, 1 H, NH), 8.12 (d, J = 9.2 Hz, 1 H, Py-4-H), 7.25 (d, J = 8.4 Hz, 2 H, Ph-3-H, Ph-5-H), 6.73 (d, J = 8.4 Hz, 2 H, Ph-2-H, Ph-6-H), 6.61 (d, J = 9.4 Hz, 1 H, Py-3-H), 4.50 (s, 2 H, PhCH$_2$); EI-MS (70 eV), m/z (%) 245 ([M$^+$], 1).

3.1.2.24. General procedure for phenolethers (**28**–**32**)

3-Piperidinopropyl chloride · HCl (**2**) (0.5 g, 2.5 mmol), K_2CO_3 (1.4 g, 10 mmol), a catalytic amount of KI and the phenol derivative (2.5 mmol) were refluxed in 20 mL DMF for 12 h. The solvent was evaporated in vacuum, the residue was dissolved in ethylacetate and the organic layer was washed with water. After removal of the solvent under reduced pressure, the residue was purified by silica column chromatography. The resulting oil was crystallized as oxalate from EtOH/Et_2O.

3.1.2.24.1. N-(4-[3-Piperidinopropoxy]phenyl)-2-amino-5-nitropyridine dihydrogen oxalate (**28**)

[Eluent, ethyl acetate/TEA/petroleum ether (95 : 5 : 100)]. Yield: 36%; ^{1}H NMR ([D$_6$]DMSO) δ 9.97* (s, 1 H, NH), 8.98 (s, 1 H, Py-6-H), 8.22 (d, J = 9.3 Hz, 1 H, Py-4-H), 7.54 (d, J = 8.8 Hz, 2 H, Ph-3-H, Ph-5-H), 6.93 (d, J = 8.9 Hz, 2 H, Ph-2-H, Ph-6-H), 6.78 (d, J = 9.3 Hz, 1 H, Py-3-H), 3.98 (t, J = 6.3 Hz, 2 H, CH_2O), 2.32–2.43 (m, 6H, 2Pip-2-H, 2Pip-6-H, $PipCH_2$), 1.85 (m, 2 H, $PipCH_2CH_2$), 1.45–1.50 (m, 6 H, 2Pip-3-H, 2Pip-4-H, 2Pip-5-H); EI-MS (70 eV), m/z (%) 356 ([M$^+$], 3).

3.1.2.24.2. *N*-(4-[3-Piperidinopropoxy]benzyl)-2-amino-5-nitropyridine hydrogen oxalate (**29**)

[Eluent, ethyl acetate/TEA/petroleum ether (95 : 5 : 100)]. Yield: 61%; ^{1}H NMR ([D$_6$]DMSO) δ 8.90 (s, 1 H, Py-6-H), 8.53 (s, 1 H, NH), 8.13 (d, J = 7.8 Hz, 1 H, Py-4-H), 7.26 (d, J = 8.4 Hz, 2 H, Ph-3-H, Ph-5-H), 6.90 (d, J = 8.4 Hz, 2 H, Ph-2-H, Ph-6-H), 6.60 (d, J = 7.8 Hz, 1 H, Py-3-H), 4.54 (s, 2 H, $PhCH_2$), 4.01 (t, J = 5.8 Hz, 2 H, CH_2O), 3.14 (m, 6 H, $PipCH_2$, 2Pip-2-H, 2Pip-6-H), 2.10 (m, 2 H, $PipCH_2CH_2$), 1.55–1.73 (m, 6 H, 2Pip-3-H, 2Pip-4-H, 2Pip-5-H); FAB$^+$-MS (Xe, DMSO/m-NO_2-Benzylalkohol), m/z (%) 371 ([M + H$^+$], 52).

3.1.2.24.3. *N*-(2-[4-(3-Piperidinopropoxy)phenyl]ethyl)-2-amino-5-nitropyridine dihydrogen oxalate (**30**)

[Eluent, ethyl acetate/TEA/petroleum ether (95 : 5 : 150)]. Yield 40%; ^{1}H NMR (CF_3COOD) δ 8.98 (s, 1 H, Py-6-H), 8.66 (d, J = 7.6 Hz, 1 H, Py-4-H), 7.24 (d, J = 8.4 Hz, 2H, Ph-3-H, Ph-5-H), 7.18 (d, 1 H, Py-3-H), 6.93 (d, J = 8.6 Hz, 2 H, Ph-2-H, Ph-6-H), 4.30 (t, J = 5.2 Hz, 2 H, CH_2O), 3.86 (m, 4 H, Pip-2-H$_{äq}$, Pip-6-H$_{äq}$, $PhCH_2CH_2$), 3.51 (m, 2 H, $PipCH_2$), 3.08 (m, 4 H, Pip-2-H$_{ax}$, Pip-6-H$_{ax}$, $PhCH_2$), 2.40 (m, 2 H, $PipCH_2CH_2$), 1.93–2.19 (m, 5 H, 2Pip-3-H, Pip-4-H$_{äq}$, 2Pip-5-H), 1.68 (m, 1 H, Pip-4-H$_{ax}$); EI-MS (70 eV), m/z (%) 384 ([M$^+$], < 1).

3.1.2.24.4. *N*-(3-[4-(3-Piperidinopropoxy)phenyl]propyl)-2-amino-5-nitropyridine hydrogen oxalate (**31**)

[Eluent, ethyl acetate/TEA/petroleum ether (95 : 5 : 150 → 95 : 5 : 1)]. Yield: 88%; ^{1}H NMR ([D$_6$]DMSO) δ 8.90 (s, 1 H, Py-6-H), 8.18 (d, J = 10.3 Hz, 1 H, Py-4-H), 8.08* (s, 1 H, NH), 7.13 (d, J = 8.3 Hz, 2 H, Ph-3-H, Ph-5-H), 6.84 (d, J = 8.3 Hz, 2 H, Ph-2-H, Ph-6-H), 6.55 (d, J = 9.4 Hz, 1 H, Py-3-H), 3.99 (t, J = 5.8 Hz, 2 H, CH_2O), 3.37 (t, J = 7.1 Hz, 2 H, $Ph(CH_2)_2CH_2$), 3.12 (m, 6 H, $PipCH_2$, 2Pip-2-H, 2Pip-6-H), 2.59 (t, J = 7.6 Hz, $PhCH_2$), 2.08 (m, 2 H, $PipCH_2CH_2$), 1.52–1.86 (m, 8 H, 2Pip-3-H, 2Pip-4-H, 2Pip-5-H, $PhCH_2CH_2$); EI-MS (70 eV), m/z (%) 398 ([M$^+$], < 1).

3.1.2.24.5. *N*-(4-[4-(3-Piperidinopropoxy)phenyl]butyl)-2-amino-5-nitropyridine hydrogen oxalate (**32**)

[Eluent, ethyl acetate/TEA/petroleum ether (95 : 5 : 150 → 95 : 5 : 1)]. Yield: 34%; ^{1}H NMR ([D$_6$]DMSO) δ 8.89 (s, 1H, Py-6-H), 8.15 (d, J = 10.5 Hz, 1H, Py-4-H), 8.06* (s, 1H, NH), 7.10 (d, J = 8.4 Hz, 2H, Ph-3-H, Ph-5-H), 6.83 (d, J = 8.4 Hz, 2H, Ph-2-H, Ph-6-H), 6.53 (d, J = 9.4 Hz, 1H, Py-3-H), 3.98 (t, J = 5.8 Hz, 2H, CH_2O), 3.38 (t, J = 7.0 Hz, 2H, $Ph(CH_2)_3CH_2$), 3.12 (m, 6H, $PipCH_2$, 2Pip-2-H, 2Pip-6-H), 2.54 (t, J = 6.8 Hz, $PhCH_2$), 2.08 (m, 2H, $PipCH_2CH_2$), 1.54–1.72 (m, 10H, 2Pip-3-H, 2Pip-4-H, 2Pip-5-H, $PhCH_2(CH_2)_2$); EI-MS (70 eV), m/z (%) 412 ([M$^+$], < 1).

3.1.2.25. General procedure for hydrogenation

A solution of **30**, **31** or **32** in 20 mL THF and 50 mg Pd/C (10%) was hydrogenated (1 bar) for 12 h. After filtering and evaporating of the solvent, the residue was purified by silica gel chromatography using ethyl acetate/TEA/methanol (95 : 5 : 5).

3.1.2.25.1. N^2-(2-[4-(3-Piperidinopropoxy)phenyl]ethyl)-2,5-diaminopyridine dihydrogen oxalate (**33**)

From **30** (0.39 g, 1 mmol); [Eluent, methylene chloride/methanol (98 : 2; ammonia atmosphere)]. Yield: 42%; ^{1}H NMR (CF_3COOD) δ 8.60 (s, 1 H, Py-6-H), 8.12 (d, J = 9.1 Hz, 1 H, Py-4-H), 7.25 (d, J = 8.5 Hz, 2 H, Ph-3-H, Ph-5-H), 7.13 (d, J = 9.8 Hz, 1H, Py-3-H), 6.92 (d, J = 8.5 Hz, 2 H, Ph-2-H, Ph-6-H), 6.91 (br, 1H, NH), 4.31 (t, J = 5.2 Hz, 2 H, CH_2O), 3.88 (m, 2 H, Pip-2-H$_{äq}$, Pip-6-H$_{äq}$), 3.78 (t, J = 6.5 Hz, 2 H, $PhCH_2CH_2$), 3.51 (t, J = 5.9 Hz, 2 H, $PipCH_2$), 3.07 (m, 4 H, Pip-2-H$_{ax}$, Pip-6-H$_{ax}$, $PhCH_2$), 2.40 (m, 2 H, $PipCH_2CH_2$, 1.93–2.19 (m, 5 H, 2Pip-3-H, Pip-4-H$_{äq}$, 2Pip-5-H), 1.68 (m, 1 H, Pip-4-H$_{ax}$); EI-MS (70 eV), m/z (%) 354 ([M$^+$], 12).

3.1.2.25.2. N^2-(3-[4-(3-Piperidinopropoxy)phenyl]propyl)-2,5-diaminopyridine trihydrogen oxalate (**34**)

From **31** (0.5 g, 1.6 mmol); [Eluent, methylene chloride/methanol (98 : 2)]. Yield: 11%; ^{1}H NMR (CF_3COOD) δ 8.43 (s, 1 H, Py-6-H), 8.15 (br, 1 H, Py-4-H), 7.21 (m, 3 H, Ph-3-H, Ph-5-H, NH), 6.90 (m, 3 H, Ph-2-H, Ph-6-H, Py-3-H), 4.33 (t, J = 5.0 Hz, 2 H, CH_2O), 3.88 (m, 2 H, Pip-2-H$_{äq}$, Pip-6-H$_{äq}$), 3.50 (m, 4 H, $PipCH_2$, $Ph(CH_2)_2CH_2$), 3.04 (m, 2 H, Pip-2-H$_{ax}$, Pip-6-H$_{ax}$), 2.81 (t, J = 7.1 Hz, 2 H, $PhCH_2$), 2.40 (m, 2 H, $PipCH_2CH_2$), 1.89–2.20 (m, 7 H, 2Pip-3-H, Pip-4-H$_{äq}$, 2Pip-5-H, $PhCH_2CH_2$), 1.66 (m, 1 H, Pip-4-H$_{ax}$); EI-MS (70 eV), m/z (%) 368 ([M$^+$], 25).

3.1.2.25.3. N^2-(4-[4-(3-Piperidinopropoxy)phenyl]butyl)-2,5-diaminopyridine trihydrogen oxalate (**35**)

From **32** (0.5 g, 1.2 mmol); [Eluent, methylene chloride/methanol (8 : 2)]. Yield: 28%; ^{1}H NMR (CF_3COOD) δ 8.45 (s, 1 H, Py-6-H), 8.16 (br, 1 H, Py-4-H), 7.21 (d, J = 8.1 Hz, 3 H, Ph-3-H, Ph-5-H, NH), 6.88 (d, J = 8.1 Hz, 3H, Ph-2-H, Ph-6-H, Py-3-H), 4.34 (t, J = 5.0 Hz, 2 H, CH_2O), 3.90 (m, 2 H, Pip-2-H$_{äq}$, Pip-6-H$_{äq}$), 3.52 (m, 4 H, $PipCH_2$, $Ph(CH_2)_3CH_2$), 3.04 (m, 2 H, Pip-2-H$_{ax}$, Pip-6-H$_{ax}$), 2.72 (m, 2 H, $PhCH_2$), 2.40 (m, 2 H, $PipCH_2CH_2$), 1.80–2.19 (m, 9H, 2Pip-3-H, Pip-4-H$_{äq}$, 2Pip-5-H, $PhCH_2(CH_2)_2$), 1.66 (m, 1 H, Pip-4-H$_{ax}$); EI-MS (70 eV), m/z (%) 382 ([M$^+$], 16).

3.2. Pharmacology

3.2.1. [^{125}I]Iodoproxyfan binding assay

In brief, cells stably transfected with the human H_3 receptor CHO-K1 were washed and harvested with a PBS medium (Ligneau et al. 1994; Ligneau et al. 2000). 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, 50 mM, 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 were incubated with [^{125}I]iodoproxyfan (25–30 pM) for 60 min at 25 °C alone or together with competing drugs dissolved the same buffer to give a final volume of 200 µL. Incubations were performed in triplicate and stopped by four additions of 5 mL of ice-cold phosphate buffer, followed by rapid filtration through glass microfiber filters (GF/B Whatman, Clifton, NJ) presoaked in 0.3% polyethylenimine. Radioactivity trapped on the filters was measured with a LKB (Rockville, MD) gamma counter (82% efficiency). Specific binding was defined as that inhibited by 1 µM imetit, a specific H_3 receptor agonist. K_i values were determined according to Cheng-Prusoff equation (Cheng and Prusoff 1973).

3.2.2. Inhibition of histamine N$^\tau$-methyltransferase (HMT)

As described by Apelt et al. (2002), 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. (1983) with minor modification (Garbarg et al. 1989). 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. The value given is the mean ± SEM.

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