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Structural variations of 1-(4-(phenoxymethyl)benzyl)piperidines as nonimidazole histamine H_3 receptor antagonists

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Abstract—Recent bioisoteric replacements in histamine H_3 receptor ligands with an exchange of the imidazole moiety by a piperidino group as well as of the trimethylene chain in 4-((3-phenoxy)propyl)-1*H*-imidazole derivatives (proxifan class) by an α,α′-xylendiyl linker represents the starting point in the development of 1-(4-(phenoxymethyl)benzyl)piperidines as a new class of nonimidazole histamine H_3 receptor antagonists. According to different strategies in optimization of imidazole-containing antagonists the central benzyl phenyl ether moiety was replaced by numerous other polar functionalities. Additionally, the *ortho*- and *meta*-analogues of the lead were synthesized to determine the influence of the position of the piperidinomethyl substituent. The new compounds were tested in an in vitro binding assay for their affinities for cloned human H_3 receptors stably expressed in CHO-K1 cells and for their oral in vivo potencies brain in a functional screening assay in the brain of mice. Additionally, activities of selected compounds were determined in the guinea-pig ileum functional test model. In contrast to the analogues *ortho*-substituted compounds all other compounds maintained respectable affinities for the human H_3 receptor ($-\log K_i$ values 6.3–7.5). Despite the results from other classes of compounds the 4-methyl substituted derivatives generally displayed higher affinities than the corresponding 4-chloro substituted compounds. In vivo only the inverse phenyl benzyl ether (**3**) showed worthwhile antagonist potencies.

1. Introduction

The neurotransmitter histamine inhibits its own release[1] and synthesis[2] in the central nervous system (CNS) via presynaptically located H_3 autoreceptors and modulates the release of numerous other neurotransmitters.[3–6] Since the recent successful cloning of rodent[7] and especially human H_3 receptors[8] many important new findings in this research field have been reported. Multiple isoforms of the H_3 receptor,[9] differential isoform distribution in the brain of rodent[10] and man,[11] constitutive activity in vivo,[12] and very recently a related fourth histamine receptor subtype have been identified.[13]

The involvement of histamine in several (patho)physiological processes is discovered in more detail. Since cipralisant (GT-2331) has entered phase II clinical trials for the treatment of attention-deficit hyperactivity disorder and the Abbott compound ABT-834 is also in early clinical trials for cognitive disorders or as an anti-obesity agent,[14–16] the formerly predicted therapeutic use of H_3 receptor antagonists in psychiatric diseases and other disorders of the CNS[17] is eagerly awaited to be confirmed. Therefore, it is of growing interest to discover ligands with high potency and selectivity, not only to characterize receptor subtypes and to determine structure–activity relationships, but also to maintain their practical use by performing CNS availability after

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per oral application.[16] Since many imidazole-containing compounds, for example, cimetidine, possess unwanted interactions with CYP 450 isoenzymes we focused on the replacement of the imidazole moiety by alicyclic amines in many classes of H_3 receptor ligands.[18] This led to the discovery of UCL 2190 (K_i (human) = 1.5 nM, ED_{50} (mouse) = 0.18 mg/kg p.o.) as a potent nonimidazole analogue of ciproxifan.[19–21] Interestingly, it was recently reported that some nonimidazole H_3 receptor antagonists do not possess affinity for H_4 receptors whereas most imidazole-containing antagonists tested displayed more or less comparable affinities for H_3 and H_4 receptors.[22]

Based on a 4-((1*H*-imidazol-4-yl)methyl)benzyl template[23] reported for a new class of imidazole-containing antagonists we have designed related nonimidazole compounds by simple replacement of the imidazole ring by a piperidino moiety leading to 1-(4-(phenoxymethyl)benzyl)piperidines.[24] In an extension of previous investigations on the substitution pattern of these compounds here we report on variations of the functionality and of substituents (Fig. 1).

By analogy with previous concepts to improve imidazole-containing antagonists, inverse ethers, amines, esters, carbamates and dibenzyl ethers were synthesized. Furthermore the *ortho*- and *meta*-analogues of the lead compounds **1** and **2** were prepared to determine the influence of the position of the piperidinomethyl substituent. Thus we have studied a novel series of piperidines in which the chemical structures possess two lipophilic moieties connected by a polar functionality.

All compounds were screened for their affinities at the human histamine H_3 receptor stably expressed in CHO-K1 cells.[25,26] In vivo potency was determined by measuring the level of the main histamine metabolite, N^{τ}-methylhistamine, in the cerebral cortex after per oral administration to mice.[27] Selected compounds were also tested in a functional model for H_3 receptor potency on isolated organs of guinea-pig.[28]

2. Results and discussion

2.1. Chemistry

The inverse ether compounds **3** and **4** were obtained by reaction of the corresponding phenol **1a** either with 4-chlorobenzyl alcohol using Mitsunobu procedure[29] or with 4-methylbenzyl bromide by performing a classical Williamson ether synthesis (Scheme 1). 4-(Piperidinomethyl)phenylmethanol (**3a**) was prepared from 4-formylbenzoic acid methyl ester as reported previously.[24] Amines **5** and **6** were prepared from terephthalaldehyde mono(diethyl acetal). The aldehyde was reductively aminated with either piperidine or 4-chloroaniline, and then the protecting group was cleaved under acidic work-up conditions resulting in the intermediate products **5a** and **6a**, respectively. In the second similar step these intermediates were again reductively aminated with 4-methylaniline or piperidine to the final compounds, respectively. Using phase transfer catalysis **3a** reacted with the corresponding benzyl chlorides to the dibenzyl ether derivatives **7**–**10**.[30] Esters (**11**, **12**) and carbamates (**13**, **14**) were synthesized, respectively, from **3a** and the corresponding benzoyl chlorides and isocyanates, respectively (Scheme 1).[31]

For compounds with the amino moiety in the *meta*-position (**15**, **16**) the *meta*-analogue of **3a** was required: this was prepared by analogous reductive amination of isophthaldialdehyde, which resulted in the phenyl methanol precursor **15a** through simultaneous reduction of the remaining aldehyde functionality to the alcohol under the conditions selected (Scheme 2). Compound **15a** was then used to prepare the final compounds **15** and **16** via Mitsunobu reaction. The same synthetic route using phthaldialdehyde to synthesize the *ortho*-substituted precursor **17a** led to compound **17**. Unexpectedly this method failed to provide the chloro compound **18.** So an alternative route was selected. 4-Chlorophenol was treated with an excess of *ortho*-α,α′-dibromoxylene in a S_N reaction to give the intermediate **18a**, which was then used to alkylate piperidine (Scheme 2).

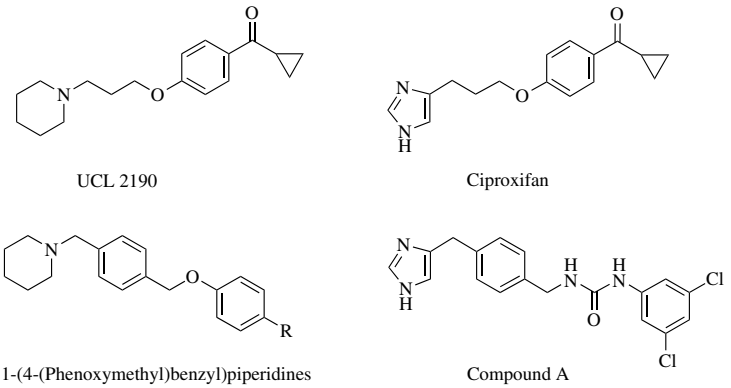
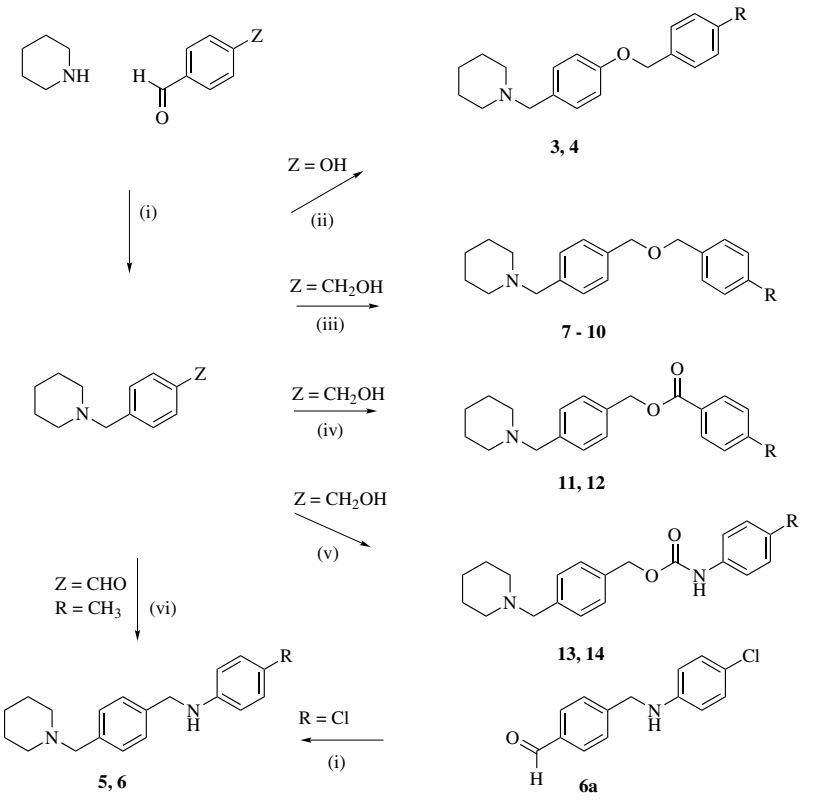
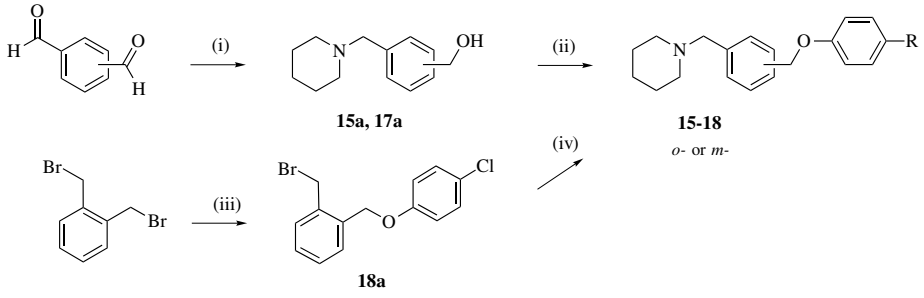


Figure 1. Imidazole and nonimidazole histamine H_3 receptor antagonists.



Scheme 1. Synthesis of precursors **1a**, **5a**, **6a** and final compounds **3**–**14** (for residue R please refer to Table 1). Reagents and conditions: (i) $Ti[OCH(CH_3)_2]_4$, $NaBH_3CN$, EtOH, 12 h, rt; (ii) **3**: 4-methylbenzyl bromide, KOH, EtOH, 48 h, reflux; **4**: 4-chlorobenzyl alcohol, DEAD, PPh_3, THF, 3 d, rt; (iii) NaOH (40%), $TBAHSO_4$, toluol, 12 h, rt; (iv) triethylamine, THF, 5 h, rt; (v) corresponding isocyanate, THF, N_2, 4 h, rt; (vi) 4-methylaniline, $Ti[OCH(CH_3)_2]_4$, $NaBH_4$, EtOH, 12 h, rt; **3**–**4**: 1-(4-hydroxybenzyl)piperidine (**1a**); **7**–**14**: 4-(piperidinomethyl)phenylmethanol (**3a**); **5**: 4-(piperidinomethyl)benzaldehyde (**5a**); **6**: piperidine; **6a**: terephthalaldehyde mono(diethyl acetal), 4-chloroaniline, $Ti[OCH(CH_3)_2]_4$, $NaBH_3CN$, EtOH, 12 h, rt.



Scheme 2. Synthesis of precursors **15a**, **17a**, **18a** and final compounds **15**–**18** (for residue R please refer to Table 1). Reagents and conditions: (i) piperidine, $Ti[OCH(CH_3)_2]_4$, $NaBH_4$, EtOH, 9 h, rt; (ii) DEAD, PPh_3, corresponding phenol, THF, 3 d, rt; (iii) 4-chlorophenol, K_2CO_3, EtOH, 12 h reflux; (iv) piperidine, KOH, EtOH, 12 h, reflux.

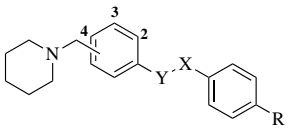
2.2. Pharmacological results and discussion

2.2.1. In vitro binding assay at cloned human H_3 receptors. The affinities of compounds were determined by measuring the displacement curves of [^{125}I]iodoproxyfan at human histamine H_3 receptors stably expressed in CHO cells (Table 1).[25,26]

All compounds having a *para*- or *meta*-substituted phenyl spacer instead of the trimethylene chain showed moderate to good affinities for the human histamine H_3 receptor. The analogous *ortho*-substituted compounds **17** and **18** showed a dramatic loss of affinities, whereas the *meta*-substituted derivatives **15** and **16** still showed moderate, but lower affinities than those of the corresponding *para*-substituted lead compounds **1** and **2**.

Comparing the different polar functionalities (–Y–X–) connecting the lipophilic moieties for the *para*-substituted compounds it is seen that the inverse ether compounds **3** and **4**, the esters **11** and **12** and the carbamates **13** and **14** show surprisingly small variation in affinity

Table 1. Chemical structures and antagonist potencies of benzylpiperidines at histamine H_3 receptors



No	P[a]	Y	X	R	$-\log K_i$[b]	$ED_{50} \pm SEM$[c] (mg/kg) p.o.	pA_2[d]
1[e]	4	CH_2	O	CH_3	6.9	1.8 ± 0.4	<6.5
2[e]	4	CH_2	O	Cl	6.9	>10	
3	4	O	CH_2	CH_3	7.4	2.4 ± 0.5	6.3
4	4	O	CH_2	Cl	7.1	≈25	6.4
5	4	CH_2	NH	CH_3	7.1	12 ± 2	6.3
6	4	CH_2	NH	Cl	6.9	>10	
7	4	CH_2	O–CH_2	H	6.7	>10	
8	4	CH_2	O–CH_2	F	6.6	>10	
9	4	CH_2	O–CH_2	Cl	6.8	>10	6.3
10	4	CH_2	O–CH_2	Br	6.7	>10	
11	4	CH_2	O–C(=O)	CH_3	7.4	⩾10	6.3
12	4	CH_2	O–C(=O)	Cl	6.6	>10	
13	4	CH_2	O–C(=O)–NH	CH_3	7.1	>10	6.1
14	4	CH_2	O–C(=O)–NH	Cl	6.7	>10	
15	3	CH_2	O	CH_3	≈6.3	10 ± 2	Nd[f]
16	3	CH_2	O	Cl	6.6	>10	
17	2	CH_2	O	CH_3	<6	>10	Nd[f]
18	2	CH_2	O	Cl	≈6	>10	
Proxyfan					8.6[g]	>10[h]	
Ciproxifan					7.3[g]	0.14[i]	8.4[i]
UCL 2190					8.8	0.18[j]	7.9[j]
Thioperamid					7.2[g]	1.0[i]	8.3[k]

[a] P position of substitution.
[b] [^{125}I] Iodoproxyfan binding assay with membranes from CHO-K1 cells stably expressing the human H_3 receptor (SEM ⩽ 0.2).[25,26]
[c] Central H_3 receptor assay in vivo after p.o. administration to mice.[27]
[d] Functional H_3 receptor in vitro assay on guinea-pig ileum (SEM ⩽ 0.2).[28]
[e] Ref. 24.
[f] Nd not determinable.
[g] Ref. 32.
[h] Ref. 34.
[i] Ref. 20.
[j] Ref. 18.
[k] Ref. 33.

values. Despite previous findings in other imidazole-containing classes of H_3 receptor antagonists[34–36] a slight preference for methyl instead of chloro substitution was found with all compounds having a *para*-substituted phenyl spacer. The most potent compounds in this series (**3**, **5**, **11** and **13**) have similar affinities to that of the reference compound ciproxifan, but do not reach the high affinities of UCL 2190 or proxyfan. In the series of ethers with dibenzyl partial structure (**7**–**10**) no influence of the different halogen substituents was observed when compared to compound **9**.

2.2.2. In vivo screening on Swiss mice. Since compounds are required to express activities in the CNS, it is of major importance for their drug-like properties that they reach their target after oral absorption. All novel compounds were screened for their modulating effects on levels of the main metabolite of histamine, N^{τ}-methylhistamine, in the brain cortex of Swiss mice after oral administration (Table 1).[27] In contrast to the comparable in vitro results of the *para*-methyl (**1**) and *para*-chloro substituted phenoxy (**2**) compounds, compound **1** only exhibited good potency in mice. The chloro compound **2** was dramatically less active in vivo. Comparable results were obtained but at a lower level with the *meta*-substituted phenyl spacer compounds **15** and **16**. The inverse ethers (**3**, **4**) showed a similar pattern, whereas all other functionalities tested (**5**–**14**) led to inactive compounds in vivo. It is unclear at the moment if pharmacokinetic reasons or different kinds of receptor antagonism (neutral antagonists vs inverse agonists) are the reason for this failure of in vivo activity. Comparable observations were made in the series of proxifans.[34]

2.2.3. Screening of selected compounds at the guinea-pig H_3 receptor. Based on the results of the methyl substituted compounds in the in vitro binding and/or in the in vivo experiments selected compounds were additionally screened for their ability to block histamine H_3 receptor agonist-induced relaxation of field-stimulated guinea-

pig ileum segments in a functional assay.[28] Apart from compounds **1**, **15** and **17**, which were not exactly determinable due to strong cross interaction with muscarinic M_3 receptors in this test model, all compounds tested were found to be antagonists with lower affinities for the guinea-pig H_3 receptor than were obtained for the human receptor. The affinities were also all similar having pA_2-value ranging from 6.1 to 6.4.

3. Conclusion

Recently developed 1-(4-phenoxymethyl)benzyl)piperidines, which are a new class of nonimidazole histamine H_3 receptor antagonists, have provided the basis for an investigation of different structural aspects in this series. Substitution patterns of the phenyl spacer seems to be less favourable with *meta*- and even worse with *ortho*-relative to *para*-substitution: Replacement of the methoxy linker of the leads **1** and **2** by other structural groups led to compounds with higher affinities at the human H_3 receptor in the case of oxymethyl and carboxylic ester compounds having a methyl substituent in the phenyl group (**3**, **11**). Their affinities for the hH_3 receptor are in the same range as that of the reference antagonist ciproxifan. Chloro substitution seems to be less favourable in this class. Preference for the methyl substitution was also seen with the in vivo screening. Unfortunately, the amino (**5**, **6**), dibenzyl (**7**–**10**), ester (**11**, **12**) and carbamate (**13**, **14**) compounds were found to be inactive in vivo in mice. The most promising compound in this series was the inverse ether compound **3** representing nanomolar affinity at the human histamine H_3 receptor and good antagonist potency in vivo.

4. Experimental

4.1. Chemistry

4.1.1. General procedures. Melting points were determined on an Electrothermal IA 9000 digital or a Büchi 512 apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker DPX 400 Avance spectrometer (400 MHz). ^{1}H NMR chemical shifts are expressed in ppm downfield from internal tetramethylsilane as reference. Data are reported in the following order: multiplicity (br, broad; s, singlet; d, doublet; t, triplet; m, multiplet; approximate coupling constants in hertz (Hz); number of protons; H_{ax}, axial proton; H_{eq}, equatorial proton; Anil, aminophenyl; Pip, piperidino; Ph, phenyl; Xyl, *para*-α,α′-xylenediyl). Mass spectra were obtained on Finnigan MAT CH7A (EI-MS) and Finnigan MAT 711 (high-resolution mass spectra), spectrometer resolving power 12,500. Elemental analyzes (C, H, N) for all compounds were measured on Perkin–Elmer 240 B or Perkin–Elmer 240 C instruments and are within ±0.4% of theoretical values (Table 2).

4.1.2. 4-Piperidinomethylphenol (1a). 4-Hydroxybenzaldehyde (3.66 g, 30 mmol), piperidine (3 mL, 30 mmol) and titanium(IV)-isopropoxide (11.2 mL, 37.5 mmol) were dissolved in 50 mL of dry ethanol and stirred for 4 h at room temperature. $NaBH_3CN$ (1.26 g, 20 mmol) was added and the mixture was additionally stirred for 12 h. After adding water the solution was filtered and concentrated in vacuo. The residue was purified by flash column chromatography (eluent: EtOAc/hexane/triethylamine 1:1:0.02) and a yellow solid was obtained (67.5%). Mp 139 °C.[37] ^{1}H NMR (CF_3COOD): δ 7.37 (d, $J = 8.5$ Hz, 2H, Ph-3-H, Ph-5-H), 7.11 (d, $J = 8.5$ Hz, 2H, Ph-2-H, Ph-6-H), 6.66 (br, 1H, N^+–H), 4.30 (d, $J = 4.9$ Hz, 2H, CH_2–N), 3.67 (d, $J = 12.0$ Hz, 2H, Pip-2-H_{eq}, Pip-6-H_{eq}), 2.97–3.05 (m, 2H, Pip-2-H_{ax}, Pip-6-H_{ax}), 2.09 (d, $J = 15.1$ Hz, 2H, Pip-3-H_{eq}, Pip-5-H_{eq}), 1.99 (d, $J = 13.9$ Hz, 1H, Pip-4-H_{eq}), 1.80–1.90 (m, 2H, Pip-3-H_{ax}, Pip-5-H_{ax}), 1.54–1.63 (m, 1H, Pip-4-H_{ax}); MS (70 eV), m/z (%) 191 ($M^{+\cdot}$, 7). Anal. ($C_{12}H_{17}NO$).

4.1.3. 1-(4-(4-Methylbenzyloxy)benzyl)piperidine (3). Compound **1a** (0.57 g, 3 mmol), 4-methylbenzylbromide (0.74 g, 4 mmol) and KOH (0.5 g, 9 mmol) were

Table 2. Physical properties and elemental analysis of final compounds **3**–**18**

No	Formula	M_w (g/mol)	Mp (°C)	Calcd (%)			Found (%)		
				C	H	N	C	H	N
3	$C_{20}H_{25}NO{\cdot}C_2H_2O_4{\cdot}0.25H_2O$	389.7	149	67.81	7.06	3.59	67.67	6.77	3.54
4	$C_{19}H_{22}ClNO{\cdot}C_2H_2O_4{\cdot}0.25H_2O$	410.1	137	61.46	5.97	3.41	61.39	5.82	3.33
5	$C_{20}H_{25}N_2{\cdot}1.5C_2H_2O_4{\cdot}0.25H_2O$	433.7	154–156	63.70	6.80	6.46	63.83	6.82	6.12
6	$C_{19}H_{23}ClN_2{\cdot}C_2H_2O_4$	404.6	153	61.56	6.09	6.77	61.95	6.20	6.63
7	$C_{20}H_{25}NO{\cdot}C_2H_2O_4{\cdot}0.25H_2O$	389.7	128–129	67.81	7.06	3.59	67.66	7.37	3.64
8	$C_{20}H_{24}FNO{\cdot}C_2H_2O_4$	403.2	125	65.54	6.45	3.47	65.37	6.24	3.44
9	$C_{20}H_{24}ClNO{\cdot}C_2H_2O_4$	419.7	161	62.96	6.19	3.34	62.95	5.93	3.28
10	$C_{20}H_{24}$ $BrNO{\cdot}C_2H_2O_4$	464.1	165–166	56.94	5.60	3.02	56.99	5.52	2.92
11	$C_{21}H_{25}NO_2{\cdot}C_2H_2O_4$	413.2	160–161	66.86	6.53	3.39	66.68	6.59	3.35
12	$C_{20}H_{22}ClNO_2{\cdot}C_2H_2O_4$	433.6	140	60.94	5.54	3.23	60.98	5.38	3.24
13	$C_{21}H_{26}N_2O_2{\cdot}C_2H_2O_4$	428.2	156–157	64.51	6.54	6.54	64.19	6.55	6.26
14	$C_{20}H_{23}ClN_2O_2{\cdot}C_2H_2O_4{\cdot}0.25H_2O$	453.1	154–155	58.31	5.62	6.18	58.30	5.48	6.14
15	$C_{20}H_{25}NO{\cdot}C_2H_2O_4$	385.2	175	68.60	7.01	3.63	68.47	6.91	3.85
16	$C_{19}H_{22}ClNO{\cdot}C_2H_2O_4$	405.6	163	62.18	5.92	3.45	62.17	5.81	3.43
17	$C_{20}H_{25}NO{\cdot}C_2H_2O_4{\cdot}0.25H_2O$	389.7	155	67.81	7.06	3.59	67.99	6.75	3.55
18	$C_{19}H_{22}ClNO{\cdot}C_2H_2O_4$	405.6	177–178	62.18	5.92	3.45	62.01	5.92	3.33

dissolved in 30 mL of ethanol and heated for 48 h under reflux. The solvent was removed in vacuo and the residue purified by flash column chromatography (eluent: EtOAc/triethylamine 99.5:0.5). The resulting orange oil was crystallized as a salt of oxalic acid from ethanol/diethyl ether (17%). ^{1}H NMR (CF_3COOD): δ 7.38 (d, $J = 8.3$ Hz, 2H, benzyl-2-H, benzyl-6-H), 7.32 (d, $J = 7.9$ Hz, 2H, Ph-2-H, Ph-6-H), 7.24 (d, $J = 7.9$ Hz, 2H, Ph-3-H, Ph-5-H), 7.11 (d, $J = 8.3$ Hz, 2H, benzyl-3-H, benzyl-5-H), 6.69 (br, 1H, N^+–H), 5.44 (s, 2H, CH_2–O), 4.30 (d, $J = 5.1$ Hz, 2H, CH_2–N), 3.67 (d, $J = 12.3$ Hz, 2H, Pip-2-H_{eq}, Pip-6-H_{eq}), 2.96–3.08 (m, 2H, Pip-2-H_{ax}, Pip-6-H_{ax}), 2.37 (s, 3H, CH_3), 2.09 (d, $J = 14.6$ Hz, 2H, Pip-3-H_{eq}, Pip-5-H_{eq}), 1.99 (d, $J = 13.5$ Hz, 1H, Pip-4-H_{eq}), 1.81–1.91 (m, 2H, Pip-3-H_{ax}, Pip-5-H_{ax}), 1.47–1.53 (m, 1H, Pip-4-H_{ax}); MS (70 eV), m/z (%) 295 ($M^{+\cdot}$, 12).

4.1.4. 1-(4-(4-Chlorobenzyloxy)benzyl)piperidine (4). Compound **1a** (0.57 g, 3 mmol), 4-chlorobenzylalcohol (0.43 g, 3 mmol) and triphenylphosphine (0.78 g, 3 mmol) were dissolved in 20 mL of dry tetrahydrofuran under argon atmosphere and cooled in an ice bath. Diethyl azodicarboxylate (DEAD, 0.57 mL, 3.6 mmol) was added dropwise followed by stirring for 3 d at room temperature. The solvent was removed in vacuo and the residue was purified by flash column chromatography (eluent: EtOAc/hexane/triethylamine 1:1:0.02). The product obtained was crystallized as a salt of oxalic acid from ethanol/diethyl ether (16%). ^{1}H NMR (CF_3COOD): δ 7.34–7.44 (m, 6H, benzyl-2-H, benzyl-3-H, benzyl-5-H, benzyl-6-H, Ph-3-H, Ph-5-H), 7.17 (d, $J = 8.5$ Hz, 2H, Ph-2-H, Ph-6-H), 6.68 (br, 1H, N^+–H), 5.21 (s, 2H, CH_2–O), 4.30 (d, $J = 4.9$ Hz, 2H, CH_2–N), 3.67 (d, $J = 11.9$ Hz, 2H, Pip-2-H_{eq}, Pip-6-H_{eq}), 2.95–3.03 (m, 2H, Pip-2-H_{ax}, Pip-6-H_{ax}), 2.08 (d, $J = 14.3$ Hz, 2H, Pip-3-H_{eq}, Pip-5-H_{eq}), 1.99 (d, $J = 13.6$ Hz, 1H, Pip-4-H_{eq}), 1.80–1.90 (m, 2H, Pip-3-H_{ax}, Pip-5-H_{ax}), 1.53–1.62 (m, 1H, Pip-4-H_{ax}); MS (70 eV), m/z (%) 315 (M^+, 10).

4.1.5. 4-(Piperidinomethyl)benzaldehyde (5a). Terephthalaldehyde mono(diethyl acetal) (20 mL, 96 mmol), piperidine (8.2 mL, 96 mmol) and titanium(IV)-isopropoxide (35.7 mL, 120 mmol) were dissolved in 50 mL of dry ethanol and stirred for 12 h at room temperature. $NaBH_4$ (3.7 g, 100 mmol) was added in and the mixture was stirred for additional 12 h. After adding 50 mL of water the solution was filtered and concentrated in vacuo. The residue was purified by flash column chromatography (eluent: EtOAc/hexane/triethylamine 1:1:0.02) to give a yellow oil (87%). ^{1}H NMR (CF_3COOD): δ 10.12 (s, 1H, CHO), 8.28 (d, $J = 8.1$ Hz, 2H, Ph-2-H, Ph-6-H), 8.0 (d, $J = 8.1$ Hz, 2H, Ph-3-H, Ph-5-H), 3.99 (d, $J = 11.4$ Hz, 1H, CH_2–N), 3.85 (d, $J = 11.4$ Hz, 1H, CH_2–N), 3.41 (t, $J = 12.0$ Hz, 1H, Pip-2-H_{eq}), 3.30 (t, $J = 12.0$ Hz, 1H, Pip-6-H_{eq}), 2.15–2.25 (m, 2H, Pip-2-H_{ax}, Pip-6-H_{ax}), 1.92–2.09 (m, 5H, Pip-3-H, Pip-4-H_{eq}, Pip-5-H), 1.60–1.79 (m, 1H, Pip-4-H_{ax}); MS (70 eV), m/z (%) 203 (M^+, 83). Anal. ($C_{13}H_{17}NO$). (M_r 203.12).

4.1.6. *p*-(4-(Piperidinomethyl)benzyl)tolyl amine (5). Compound **5a** (2.03 g, 10 mmol), 4-methylaniline (1.07 g, 10 mmol) and titanium(IV)-isopropoxide (3 mL, 12 mmol) were dissolved in 60 mL of dry ethanol and stirred at room temperature for 4 h. $NaBH_4$ (0.37 g, 10 mmol) was added and the mixture was stirred for additional 12 h. Water was added and the solution was filtered. The aqueous solution was added dropwise to 200 mL of 2 N HCl and stirred for 12 h. The alcohol was evaporated and the remaining aqueous solution extracted with ethyl acetate (3×50 mL). The organic layers were combined, dried (Na_2SO_4) and the solvent was removed in vacuo. The residue was purified by flash column chromatography (eluent: EtOAc/hexane/triethylamine 1:1:0.02) and the product obtained was crystallized as a salt of oxalic acid from ethanol/diethyl ether (4%). ^{1}H NMR (CF_3COOD): δ 9.97 (s, 1H, CHO), 7.54–7.62 (m, 4H, Xyl-2-H, Xyl-3-H, Xyl-5-H, Xyl-6-H), 7.40 (d, $J = 8.1$ Hz, 2H, Ph-3-H, Ph-5-H), 7.31 (d, $J = 8.1$ Hz, 2H, Ph-2-H, Ph-6-H), 7.01 (br, 1H, N^+–H), 4.77 (s, 2H, Ph-N-CH_2), 4.41 (d, $J = 4.4$ Hz, 2H, CH_2–N), 3.67 (d, $J = 11.7$ Hz, 2H, Pip-2-H_{eq}, Pip-6-H_{eq}), 3.02–3.10 (m, 2H, Pip-2-H_{ax}, Pip-6-H_{ax}), 2.46 (s, 3H, CH_3), 2.09 (d, $J = 14.7$ Hz, 2H, Pip-3-H_{eq}, Pip-5-H_{eq}), 1.99 (d, $J = 13.6$ Hz, 1H, Pip-4-H_{eq}), 1.89–1.91 (m, 2H, Pip-3-H_{ax}, Pip-5-H_{ax}), 1.54–1.64 (m, 1H, Pip-4-H_{ax}); MS (70 eV), m/z (%) 294 ($M^{+\cdot}$, 100).

4.1.7. 4-((4-Chlorophenylamino)methyl)benzaldehyde hydrochloride (6a). Terephthalaldehyde mono(diethyl acetal) (2.1 mL, 10 mmol), 4-chloroaniline (1.27 g, 10 mmol) and titanium(IV)-isopropoxide (3.7 mL, 12.5 mmol) were dissolved in 50 mL of ethanol and stirred for 6 h at room temperature. $NaBH_3CN$ (0.42 g, 6.7 mmol) was added and the mixture was additionally stirred for 12 h. After adding 10 mL of water the solution was filtered and the alcohol was evaporated under reduced pressure. The aqueous solution was added dropwise to 20 mL of 2 N HCl and stirred for 12 h. The resulting yellow precipitate was filtered and dried (21%). Mp 192 °C. ^{1}H NMR (CF_3COOD): δ 8.27 (d, $J = 8.0$ Hz, 2H, Ph-2-H, Ph-6-H), 7.99 (d, $J = 8.0$ Hz, 2H, Ph-3-H, Ph-5-H), 7.60 (d, $J = 8.7$ Hz, 2H, Anil-3-H, Anil-5-H), 7.44 (d, $J = 8.7$ Hz, 2H, Anil-2-H, Anil-6-H), 4.81 (s, 2H, CH_2–N); MS (70 eV), m/z (%) 245 ($M^{+\cdot}$, 100). Anal. (C_{14} $H_{12}ClNO$), (M_r 245.58).

4.1.8. N-(4-Chlorophenyl)-(4-(piperidinomethyl)phenyl)-methanamine (6). Synthesized, as described for **5** from **6a** (0.56 g, 2 mmol), piperidine (0.51 mL, 6 mmol), titanium(IV)-isopropoxide (1.2 mL, 4 mmol) and $NaBH_3CN$ (0.08 g, 1.3 mmol) (24.5%). ^{1}H NMR (CF_3COOD): δ 7.53–7.64 (m, 6H, Ph-3-H, Ph-5-H, Xyl-2-H, Xyl-3-H, Xyl-5-H, Xyl-6-H), 7.44 (d, $J = 8.7$ Hz, 2H, Ph-2-H, Ph-6-H), 7.00 (br, 1H, N^+–H), 4.81 (s, 2H, Ph–CH_2–N), 4.40 (d, $J = 4.5$ Hz, 2H, CH_2–N), 3.67 (d, $J = 11.7$ Hz, 2H, Pip-2-H_{eq}, Pip-6-H_{eq}), 3.02–3.10 (m, 2H, Pip-2-H_{ax}, Pip-6-H_{ax}), 2.09 (d, $J = 14.2$ Hz, 2H, Pip-3-H_{eq}, Pip-5-H_{eq}), 1.99 (d, $J = 13.7$ Hz, 1H, Pip-4-

H_{eq}), 1.82–1.92 (m, 2H, Pip-3-H_{ax}, Pip-5-H_{ax}), 1.54–1.65 (m, 1H, Pip-4-H_{ax}); MS (70 eV), *m/z* (%) 314 ($M^{+\cdot}$, 74).

4.2. General procedure for the preparation of dibenzyl-ethers 7–10

4-(Piperidinomethyl)phenylmethanol (**3a**) (0.41 g, 2 mmol), benzylbromide (for **7**), 4-fluorobenzylchloride (for **8**), 4-chlorobenzylchloride (for **9**), 4-bromobenzyl-chloride (for **10**) (6 mmol) and tetrabutylammoniumhydrogensulfate ($TBAHSO_4$, 0.34 g, 1 mmol) were dissolved in 10 mL of toluol, 10 mL of NaOH solution (40%) was added and the mixture was vigourously stirred at room temperature for 12 h (**7**: 6 h). After adding 20 mL of water the mixture was extracted with ethyl acetate (3 × 20 mL). The organic layers were combined, dried ($NaSO_4$) and the solvent removed in vacuo. The residue was purified by flash column chromatography (eluent: ethyl acetate saturated with ammonia) and the product obtained was crystallized as a salt of oxalic acid from ethanol/diethyl ether.

4.2.1. 1-(4-(Benzyloxymethyl)benzyl)piperidine (7). 76%. ^{1}H NMR (CF_3COOD): δ 7.55 (d, $J = 7.9$ Hz, 2H, Xyl-2-H, Xyl-6-H), 7.47 (d, $J = 7.9$ Hz, 2H, Xyl-3-H, Xyl-5-H), 7.35–7.43 (m, 5H, Ph-2-H, Ph-3-H, Ph-4-H, Ph-5-H, Ph-6-H), 6.78 (br, 1H, N^+–H), 4.80 (s, 4H, $(CH_2–O)_2$), 4.37 (d, $J = 5.3$ Hz, 2H, CH_2–N), 3.66 (d, $J = 11.9$ Hz, 2H, Pip-2-H_{eq}, Pip-6-H_{eq}), 2.99–3.07 (m, 2H, Pip-2-H_{ax}, Pip-6-H_{ax}), 2.08 (d, $J = 14.6$ Hz, 2H, Pip-3-H_{eq}, Pip-5-H_{eq}), 1.98 (d, $J = 13.8$ Hz, 1H, Pip-4-H_{eq}), 1.81–1.91 (m, 2H, Pip-3-H_{ax}, Pip-5-H_{ax}), 1.54–1.63 (m, 1H, Pip-4-H_{ax}); MS (70 eV), *m/z* (%) 295 ($M^{+\cdot}$, 47).

4.2.2. 1-(4-(4-Fluorobenzyloxymethyl)benzyl)piperidine (8). 67%. ^{1}H NMR (CF_3COOD): δ 7.55 (d, $J = 7.9$ Hz, 2H, Xyl-2-H, Xyl-6-H), 7.48 (d, $J = 7.9$ Hz, 2H, Xyl-3-H, Xyl-5-H), 7.41 (q, $J_1 = 5.4$ Hz, $J_2 = 2.8$ Hz, 2H, Ph-2-H, Ph-6-H), 7.09 (t, $J = 8.7$ Hz, 2H, Ph-3-H, Ph-5-H), 6.79 (br, 1H, N^+–H), 4.79 (s, 4H, $(CH_2–O)_2$), 4.37 (d, $J = 5.3$ Hz, 2H, CH_2–N), 3.67 (d, $J = 11.9$ Hz, 2H, Pip-2-H_{eq}, Pip-6-H_{eq}), 3.00–3.08 (m, 2H, Pip-2-H_{ax}, Pip-6-H_{ax}), 2.09 (d, $J = 14.9$ Hz, 2H, Pip-3-H_{eq}, Pip-5-H_{eq}), 1.99 (d, $J = 13.6$ Hz, 1H, Pip-4-H_{eq}), 1.81–1.91 (m, 2H, Pip-3-H_{ax}, Pip-5-H_{ax}), 1.54–1.64 (m, 1H, Pip-4-H_{ax}); MS (70 eV), *m/z* (%) 313 ($M^{+\cdot}$, 40).

4.2.3. 1-(4-(4-Chlorobenzyloxymethyl)benzyl)piperidine (9). 51%. ^{1}H NMR (CF_3COOD): δ 7.55 (d, $J = 7.9$ Hz, 2H, Xyl-2-H, Xyl-6-H), 7.48 (d, $J = 7.9$ Hz, 2H, Xyl-3-H, Xyl-5-H), 7.39 (d, $J = 8.5$ Hz, 2H, Ph-3-H, Ph-5-H), 7.35 (d, $J = 8.5$ Hz, 2H, Ph-2-H, Ph-6-H), 6.80 (br, 1H, N^+–H), 4.79 (s, 4H, $(CH_2–O)_2$), 4.37 (d, $J = 5.4$ Hz, 2H, CH_2–N), 3.67 (d, $J = 11.9$ Hz, 2H, Pip-2-H_{eq}, Pip-6-H_{eq}), 3.00–3.08 (m, 2H, Pip-2-H_{ax}, Pip-6-H_{ax}), 2.09 (d, $J = 14.9$ Hz, 2H, Pip-3-H_{eq}, Pip-5-H_{eq}), 1.99 (d, $J = 13.6$ Hz, 1H, Pip-4-H_{eq}), 1.81–1.91 (m, 2H, Pip-3-H_{ax}, Pip-5-H_{ax}), 1.54–1.64 (m, 1H, Pip-4-H_{ax}); MS (70 eV), *m/z* (%) 329 ($M^{+\cdot}$, 31).

4.2.4. 1-(4-(4-Bromobenzyloxymethyl)benzyl)piperidine (10). 37%. ^{1}H NMR (CF_3COOD): δ 7.55 (d, $J = 7.7$ Hz, 4H, Xyl-2-H, Xyl-6-H, Ph-3-H, Ph-5-H), 7.47 (d, $J = 7.9$ Hz, 2H, Xyl-3-H, Xyl-5-H), 7.28 (d, $J = 8.3$ Hz, 2H, Ph-2-H, Ph-6-H), 6.79 (br, 1H, N^+–H), 4.78 (s, 4H, $(CH_2–O)_2$), 4.37 (d, $J = 5.2$ Hz, 2H, CH_2–N), 3.67 (d, $J = 11.9$ Hz, 2H, Pip-2-H_{eq}, Pip-6-H_{eq}), 2.99–3.08 (m, 2H, Pip-2-H_{ax}, Pip-6-H_{ax}), 2.09 (d, $J = 14.9$ Hz, 2H, Pip-3-H_{eq}, Pip-5-H_{eq}), 1.99 (d, $J = 13.8$ Hz, 1H, Pip-4-H_{eq}), 1.81–1.91 (m, 2H, Pip-3-H_{ax}, Pip-5-H_{ax}), 1.54–1.64 (m, 1H, Pip-4-H_{ax}); MS (70 eV), *m/z* (%) 373 ($M^{+\cdot}$, 21).

4.2.5. 4-Methylbenzoic acid 4-piperidinomethylbenzyl ester (11). 4-(Piperidinomethyl)phenylmethanol (**3a**) (0.41 g, 2 mmol) and triethylamine (0.2 g, 3.5 mmol) were dissolved in 5 mL of dry tetrahydrofuran. The solution was cooled to 0 °C in an ice bath and *p*-toluoyl chloride (0.4 mL, 3 mmol) was slowly added. The mixture was allowed to warm to room temperature and was stirred for additional 4 h. The white precipitate obtained was filtered and the solution was concentrated in vacuo. The residue was purified by flash column chromatography (eluent: EtOAc/hexane 1:1 saturated with ammonia). The resulting colorless oil was crystallized as a salt of oxalic acid from ethanol/diethyl ether (75%). ^{1}H NMR (CF_3COOD): δ 8.01 (d, $J = 8.0$ Hz, 2H, Ph-2-H, Ph-6-H), 7.64 (d, $J = 7.9$ Hz, 2H, Xyl-2-H, Xyl-6-H), 7.50 (d, $J = 7.9$ Hz, 2H, Xyl-3-H, Xyl-5-H), 7.34 (d, $J = 8.0$ Hz, 2H, Ph-3-H, Ph-5-H), 6.80 (br, 1H, N^+–H), 5.54 (s, 2H, CH_2–O), 4.38 (d, $J = 5.3$ Hz, 2H, CH_2–N), 3.71 (d, $J = 12.0$ Hz, 2H, Pip-2-H_{eq}, Pip-6-H_{eq}), 3.00–3.09 (m, 2H, Pip-2-H_{ax}, Pip-6-H_{ax}), 2.45 (s, 3H, CH_3), 2.09 (d, $J = 14.9$ Hz, 2H, Pip-3-H_{eq}, Pip-5-H_{eq}), 1.99 (d, $J = 13.7$ Hz, 1H, Pip-4-H_{eq}), 1.82–1.92 (m, 2H, Pip-3-H_{ax}, Pip-5-H_{ax}), 1.54–1.64 (m, 1H, Pip-4-H_{ax}); MS (70 eV), *m/z* (%) 323 ($M^{+\cdot}$, 40).

4.2.6. 4-Chlorobenzoic acid 4-piperidinomethylbenzyl ester (12). Synthesized, as described for **11** from 4-chlorobenzoyl chloride (0.6 mL, 5 mmol) (32%). ^{1}H NMR (CF_3COOD): δ 8.06 (d, $J = 7.2$ Hz, 2H, Ph-2-H, Ph-6-H), 7.64 (d, $J = 7.4$ Hz, 2H, Xyl-2-H, Xyl-6-H), 7.50 (d, $J = 7.2$ Hz, 4H, Ph-3-H, Ph-5-H, Xyl-3-H, Xyl-5-H), 6.79 (br, 1H, N^+–H), 5.56 (s, 2H, CH_2–O), 4.38 (d, $J = 5.0$ Hz, 2H, CH_2–N), 3.71 (d, $J = 11.9$ Hz, 2H, Pip-2-H_{eq}, Pip-6-H_{eq}), 3.00–3.08 (m, 2H, Pip-2-H_{ax}, Pip-6-H_{ax}), 2.09 (d, $J = 14.9$ Hz, 2H, Pip-3-H_{eq}, Pip-5-H_{eq}), 1.99 (d, $J = 14.2$ Hz, 1H, Pip-4-H_{eq}), 1.82–1.92 (m, 2H, Pip-3-H_{ax}, Pip-5-H_{ax}), 1.54–1.63 (m, 1H, Pip-4-H_{ax}); MS (70 eV), *m/z* (%) 343 ($M^{+\cdot}$, 35).

4.2.7. *p*-Tolyl-carbamic acid 4-piperidinomethylbenzyl ester (13). *p*-Tolyl isocyanate (0.53 g, 4 mmol) and 4-(piperidinomethyl)phenylmethanol (**3a**) (0.41 g, 2 mmol) were dissolved together in 20 mL of dry tetrahydrofuran and stirred at room temperature for 3 h under nitrogen atmosphere. The solvent was removed and the residue purified by flash column chromatography (eluent: EtOAc/hexane/triethylamine 1:1:0.02). The

resulting white solid was crystallized as a salt of oxalic acid from ethanol/diethyl ether (60%). ^{1}H NMR (CF_3COOD): δ 7.58 (d, $J = 7.9$ Hz, 2H, Ph-2-H, Ph-6-H), 7.48 (d, $J = 7.9$ Hz, 2H, Ph-3-H, Ph-5-H), 7.18 (d, $J = 8.6$ Hz, 4H, Xyl-2-H, Xyl-3-H, Xyl-5-H, Xyl-6-H), 6.80 (br, 1H, N_+–H), 5.39 (s, 2H, CH_2–O), 4.37 (d, $J = 5.4$ Hz, 2H, CH_2–N), 3.70 (d, $J = 11.4$ Hz, 2H, Pip-2-H_{eq}, Pip-6-H_{eq}), 3.00–3.09 (m, 2H, Pip-2-H_{ax}, Pip-6-H_{ax}), 2.34 (s, 3H, CH_3), 2.09 (d, $J = 14.8$ Hz, 2H, Pip-3-H_{eq}, Pip-5-H_{eq}), 1.99 (d, $J = 13.2$ Hz, 1H, Pip-4-H_{eq}), 1.82–1.92 (m, 2H, Pip-3-H_{ax}, Pip-5-H_{ax}), 1.54–1.64 (m, 1H, Pip-4-H_{ax}); MS (70 eV), m/z (%) 338 ($M^{+\cdot}$, 44).

4.2.8. (4-Chlorophenyl)carbamic acid 4-piperidinomethylbenzyl ester (14). Synthesized, as described for **13** from 4-chlorophenyl isocyanate (0.61 g, 4 mmol). The white solid was directly crystallized as a salt of oxalic acid from ethanol/diethyl ether without prior purification (36%). ^{1}H NMR (CF_3COOD): δ 7.57 (d, $J = 7.6$ Hz, 2H, Ph-2-H, Ph-6-H), 7.48 (d, $J = 7.6$ Hz, 2H, Ph-3-H, Ph-5-H), 7.33 (d, $J = 8.7$ Hz, 2H, Xyl-2-H, Xyl-6-H), 7.28 (d, $J = 8.7$ Hz, 2H, Xyl-3-H, Xyl-5-H), 6.80 (br, 1H, N^+–H), 5.38 (s, 2H, CH_2–O), 4.37 (d, $J = 4.3$ Hz, 2H, CH_2–N), 3.69 (d, $J = 12.2$ Hz, 2H, Pip-2-H_{eq}, Pip-6-H_{eq}), 3.00–3.08 (m, 2H, Pip-2-H_{ax}, Pip-6-H_{ax}), 2.09 (d, $J = 14.6$ Hz, 2H, Pip-3-H_{eq}, Pip-5-H_{eq}), 1.99 (d, $J = 13.6$ Hz, 1H, Pip-4-H_{eq}), 1.82–1.92 (m, 2H, Pip-3-H_{ax}, Pip-5-H_{ax}), 1.57–1.64 (m, 1H, Pip-4-H_{ax}); MS (70 eV), m/z (%) 358 ($M^{+\cdot}$, 48).

4.2.9. (3-(Piperidinomethyl)phenyl)methanol (15a). Isophthaldialdehyde (3 g, 22 mmol), piperidine (1 mL, 9 mmol) and titanium(IV)-isopropoxide (2.6 mL, 9 mmol) were dissolved in 20 mL of dry ethanol and stirred for 1 h at room temperature. $NaBH_4$ (0.84 g, 22 mmol) was added and the mixture was additionally stirred for 8 h. After adding 10 mL of water the solution was filtered and concentrated in vacuo. The residue was purified by flash column chromatography (eluent: EtOAc/hexane/triethylamine 1:1:0.02) and a colourless oil was obtained (46%).[38] ^{1}H NMR (CF_3COOD): δ 7.65 (d, $J = 7.7$ Hz, 1H, Xyl-5-H), 7.56–7.59 (m, 2H, Xyl-4-H, Xyl-6-H), 7.51 (d, $J = 7.7$ Hz, 1H, Xyl-2-H), 5.51 (s, 2H, CH_2–O), 4.38 (d, $J = 3.7$ Hz, 2H, CH_2–N), 3.69 (d, $J = 11.9$ Hz, 2H, Pip-2-H_{eq}, Pip-6-H_{eq}), 2.99–3.09 (m, 2H, Pip-2-H_{ax}, Pip-6-H_{ax}), 2.09 (d, $J = 14.8$ Hz, 2H, Pip-3-H_{eq}, Pip-5-H_{eq}), 1.99 (d, $J = 13.8$ Hz, 1H, Pip-4-H_{eq}), 1.82–1.92 (m, 2H, Pip-3-H_{ax}, Pip-5-H_{ax}), 1.55–1.65 (m, 1H, Pip-4-H_{ax}); MS (70 eV), m/z (%) 205 ($M^{+\cdot}$, 45). Anal. $C_{13}H_{19}NO$. (M_r 205.12).

4.2.10. 1-(3-(4-Methylphenoxymethyl)benzyl)piperidine (15). Synthesized, as described for **4** from **15a** (0.51 g, 2.5 mmol) and *p*-cresol (0.27 g, 2.5 mmol) (34%). ^{1}H NMR (CF_3COOD): δ 7.64 (d, $J = 7.8$ Hz, 1H, Xyl-5-H), 7.56–7.59 (m, 2H, Xyl-4-H, Xyl-6-H), 7.44 (d, $J = 7.5$ Hz, 1H, Xyl-2-H), 7.17 (d, $J = 8.4$ Hz, 2H, Ph-3-H, Ph-5-H), 6.96 (d, $J = 8.4$ Hz, 2H, Ph-2-H, Ph-6-H), 6.75 (br, 1H, N^+–H), 5.31 (s, 2H, CH_2–O), 4.36 (d, $J = 5.3$ Hz, 2H, CH_2–N), 3.61 (d, $J = 12.0$ Hz, 2H, Pip-2-H_{eq}, Pip-6-H_{eq}), 2.92–3.01 (m, 2H, Pip-2-H_{ax}, Pip-6-H_{ax}), 2.31 (s, 3H, CH_3), 1.96–2.07 (m, 3H, Pip-3-H_{eq}, Pip-4-H_{eq}, Pip-5-H_{eq}), 1.79–1.90 (m, 2H, Pip-3-H_{ax}, Pip-5-H_{ax}), 1.51–1.60 (m, 1H, Pip-4-H_{ax}); MS (70 eV), m/z (%) 295 ($M^{+\cdot}$, 42).

4.2.11. 1-(3-(4-Chlorophenoxymethyl)benzyl)piperidine (16). Synthesized, as described for **15** from 4-chlorophenol (0.26 g, 2 mmol) (60%). ^{1}H NMR (CF_3COOD): δ 7.65 (d, $J = 7.4$ Hz, 1H, Xyl-4-H), 7.59 (t, $J = 7.4$ Hz, 1H, Xyl-5-H), 7.54 (s, 1H, Xyl-2-H), 7.45 (d, $J = 7.4$ Hz, 1H, Xyl-6-H), 7.30 (d, $J = 7.9$ Hz, 2H, Ph-3-H, Ph-5-H), 7.00 (d, $J = 7.9$ Hz, 2H, Ph-2-H, Ph-6-H), 6.79 (br, 1H, N^+–H), 5.29 (s, 2H, CH_2–O), 4.37 (d, $J = 4.1$ Hz, 2H, CH_2–N), 3.61 (d, $J = 12.0$ Hz, 2H, Pip-2-H_{eq}, Pip-6-H_{eq}), 2.92–3.01 (m, 2H, Pip-2-H_{ax}, Pip-6-H_{ax}), 2.07 (d, $J = 14.9$ Hz, 2H, Pip-3-H_{eq}, Pip-5-H_{eq}), 1.98 (d, $J = 13.8$ Hz, 1H, Pip-4-H_{eq}), 1.80–1.90 (m, 2H, Pip-3-H_{ax}, Pip-5-H_{ax}), 1.51–1.61 (m, 1H, Pip-4-H_{ax}); MS (70 eV), m/z (%) 315 ($M^{+\cdot}$, 34).

4.2.12. (2-(Piperidinomethyl)phenyl)methanol (17a). Synthesized, as described for **15a** from phthaldialdehyde (3 g, 22 mmol). The product was obtained as an orange solid (41%). Mp 72–73 C.[38] ^{1}H NMR (CF_3COOD): δ 7.51–7.60 (m, 3H, Xyl-3-H, Xyl-4-H, Xyl-5-H), 7.49 (d, $J = 7.3$ Hz, 1H, Xyl-6-H), 5.02 (s, 2H, CH_2–O), 4.3 (d, $J = 3.5$ Hz, 2H, CH_2–N), 3.64 (d, $J = 12.2$ Hz, 2H, Pip-2-H_{eq}, Pip-6-H_{eq}), 3.01–3.07 (m, 2H, Pip-2-H_{ax}, Pip-6-H_{ax}), 2.10 (d, $J = 14.8$ Hz, 2H, Pip-3-H_{eq}, Pip-5-H_{eq}), 1.98 (d, $J = 13.3$ Hz, 1H, Pip-4-H_{eq}), 1.73–1.80 (m, 2H, Pip-3-H_{ax}, Pip-5-H_{ax}), 1.57–1.64 (m, 1H, Pip-4-H_{ax}); MS (70 eV), m/z (%) 205 ($M^{+\cdot}$, 16). Anal. ($C_{13}H_{19}O$). (M_r 205.12).

4.2.13. 1-(2-p-Tolyloxymethyl)benzylpiperidine (17). Synthesized, as described for **15** from **17a** (0.41 g, 2 mmol) (7%). ^{1}H NMR (CF_3COOD): δ 7.59–7.65 (m, 3H, Xyl-3-H, Xyl-4-H, Xyl-5-H), 7.52 (d, $J = 7.3$ Hz, 1H, Xyl-6-H), 7.27 (d, $J = 8.5$ Hz, 2H, Ph-3-H, Ph-5-H), 7.01 (d, $J = 8.5$ Hz, 2H, Ph-2-H, Ph-6-H), 6.79 (br, 1H, N^+–H), 5.30 (s, 2H, CH_2–O), 4.44 (d, $J = 5.6$ Hz, 2H, CH_2–N), 3.58 (d, $J = 12.3$ Hz, 2H, Pip-2-H_{eq}, Pip-6-H_{eq}), 3.01–3.10 (m, 2H, Pip-2-H_{ax}, Pip-6-H_{ax}), 2.36 (s, 3H, CH_3), 2.07 (d, $J = 12.8$ Hz, 2H, Pip-3-H_{eq}, Pip-5-H_{eq}), 1.98 (d, $J = 13.6$ Hz, 1H, Pip-4-H_{eq}), 1.55–1.70 (m, 3H, Pip-3-H_{ax}, Pip-4-H_{ax}, Pip-5-H_{ax}); MS (70 eV), m/z (%) 295 ($M^{+\cdot}$, 34).

4.2.14. 2-(4-Chlorophenoxymethyl)benzyl bromide (18a). *ortho*-α,α'-Dibromoxylene (5.28 g, 20 mmol) and 4-chlorophenol (0.65 g, 5 mmol) were dissolved in 150 mL of ethanol and K_2CO_3 (1.38 g, 10 mmol) was added. The mixture was heated for 12 h under reflux and filtered. The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography (eluent: dichloromethane/petrol ether 2:8) to give a colourless oil (32%). ^{1}H NMR ($CDCl_3$): δ 7.39–7.44 (m, 2H, Xyl-3-H, Xyl-5-H), 7.32–7.35 (m, 2H, Xyl-4-H, Xyl-6-H), 7.25 (d,

$J = 8.9$ Hz, 2H, Ph-3-H, Ph-5-H), 6.93 (d, $J = 8.9$ Hz, 2H, Ph-2-H, Ph-6-H), 5.17 (s, 2H, CH_2–O), 4.59 (s, 2H, CH_2–Br); MS (70 eV), m/z (%) 310 ($M^{+\cdot}$, 5). Anal. ($C_{14}H_{12}BrClO$). (M_r 311.48).

4.2.15. 1-(2-(4-Chlorophenoxymethyl)benzyl)piperidine (18). Compound **18a** (0.5 g, 1.6 mmol), piperidine (0.26 mL, 3 mmol) and KOH (0.2 g, 3 mmol) were dissolved in 20 mL of ethanol and heated for 12 h under reflux. The mixture was filtered and concentrated in vacuo. The residue was purified by flash column chromatography (eluent: dichloromethane/petrol ether 3:7). The resulting white solid was crystallized as a salt of oxalic acid from ethanol (96%). ^{1}H NMR (CF_3COOD): δ 7.60–7.68 (m, 3H, Xyl-3-H, Xyl-4-H, Xyl-5-H), 7.54 (d, $J = 7.3$ Hz, 1H, Xyl-6-H), 7.41 (d, $J = 8.9$ Hz, 2H, Ph-3-H, Ph-5-H), 7.28 (br, 1H, N^+–H), 7.07 (d, $J = 8.9$ Hz, 2H, Ph-2-H, Ph-6-H), 5.32 (s, 2H, CH_2–O), 4.47 (d, $J = 5.6$ Hz, 2H, CH_2–N), 3.61 (d, $J = 12.1$ Hz, 2H, Pip-2-H_{eq}, Pip-6-H_{eq}), 3.05–3.14 (m, 2H, Pip-2-H_{ax}, Pip-6-H_{ax}), 2.10 (d, $J = 15.0$ Hz, 2H, Pip-3-H_{eq}, Pip-5-H_{eq}), 1.99 (d, $J = 13.7$ Hz, 1H, Pip-4-H_{eq}), 1.61–1.71 (m, 3H, Pip-3-H_{ax}, Pip-4-H_{ax}, Pip-5-H_{ax}); MS (70 eV), m/z (%) 315 ($M^{+\cdot}$, 15).

4.3. Pharmacology

4.3.1. [^{125}I]Iodoproxyfan binding assay on stably transfected CHO-K1 cells. Potency of the novel compounds **7–18** was investigated in a radioligand binding assay described by Ligneau et al.[20] In brief, transfected CHO-K1 cells were washed and harvested with a PBS medium. They were centrifuged (140g, 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 (23,000g, 30 min, +4 °C) and the pellet obtained 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 for 60 min at 25 °C with [^{125}I]iodoproxyfan ($c = 25$ pmol/L) alone, or together with competing drugs dissolved in the same buffer to give a final volume of 200 μL. Incubations were performed in triplicate and stopped by four additions (5 mL) of ice-cold medium, followed by rapid filtration through glass microfibre filters (GF/B Whatman, Clifton, NJ) presoaked in polyethylene imine ($\omega =$ 0.3%). Radioactivity trapped on the filters was measured with a LKB (Rockville, MD) gamma counter (efficiency: 82%). Specific binding was defined as that inhibited by imetit ($c = 1$ μmol/L), a specific H_3 receptor agonist.[26] IC_{50} values were determined using an iterative least squares method,[39] and assuming a competitive antagonism K_i values were calculated from their IC_{50} values by using the Cheng–Prusoff equation.[40] Data are presented as the mean of experiments performed at least in triplicate.

4.3.2. Histamine H_3 receptor antagonist potency in vivo in the mouse. In vivo testing was performed after per oral administration of the test compounds to Swiss mice according to Garbarg et al.[27] Brain histaminergic neuronal activity was assessed by measuring the main metabolite of histamine, N^τ-methylhistamine. Mice were fasted for 24 h before per oral treatment. Animals were decapitated 90 min after treatment, and the cerebral cortex was isolated. The cerebral cortex was homogenized in 10 vol of ice-cold perchloric acid (0.4 M). The N^τ-methylhistamine level was measured by radioimmunoassay.[41] By treatment with 3 mg/kg ciproxifan the maximal increase in N^τ-methylhistamine level was obtained and related to the level reached with the administered drug. Each experiment was performed at least in triplicate. The ED_{50} value was calculated as mean value with SEM.[39]

4.3.3. Histamine H_3 receptor antagonist potency on guinea-pig ileum.[28] Histamine H_3 receptor antagonist potency was determined by concentration-dependent inhibition of (*R*)-α-methylhistamine induced relaxation of field-stimulated isolated guinea-pig ileum segments (longitudinal muscle with adhering plexus myentericus) in the presence of the antagonist under study according to Ligneau et al.[26] Each experiment was performed at least in triplicate. Logarithmic data are presented as mean with SEM. Longitudinal muscle strips were prepared from the small intestine, 20–50 cm proximal to the ileocaecal valve. The muscle strips were mounted between two platinum electrodes (4 mm apart) in 20 mL of Krebs buffer, containing 1 μM mepyramine, connected to an isometric transducer, continuously gassed with oxygen containing 5% CO_2 at 37 °C. After equilibration of the muscle segments for 1 h accompanied by washing every 10 min, they were stimulated continuously with rectangular pulses of 15 V and 0.5 ms at a frequence of 0.1 Hz. After 30 min of stimulation, a cumulative concentration-response curve to (*R*)-α-methylhistamine was recorded. Subsequently the preparations were washed three times every 10 min without stimulation. The antagonist was incubated 20–30 min before redetermination of the concentration-response curve of (*R*)-α-methylhistamine. The new antagonists were tested at concentrations that did not block ileal muscarinic M_3 receptors (data not shown), unless otherwise stated (please see the results and discussion section for details).

4.3.4. Muscarinic M_3 receptor assay on guinea-pig ileum. The procedure was performed as described in the literature.[42]

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