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Piperidine-containing histamine H_3 receptor antagonists of the carbamate series: the influence of the additional ether functionality

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Recently novel leads for histamine H_3 receptor antagonists of the non-imidazole type have been described. As a continuation of this research eleven new carbamate derivatives possessing an additional ether functionality were prepared. The compounds were evaluated *in vitro* for their antagonist activity on isolated organs of guinea-pig (GP) H_3 as well as H_2, H_1, and M_3 receptors, respectively. All compounds investigated possessed moderate antagonist affinities at guinea-pig histamine H_3 receptors (pA_2 6.11–6.76). An ether functionality introduced in different places of the lipophilic part of carbamates differently influenced activity and selectivity toward H_3, M_3, and other histamine receptors tested.

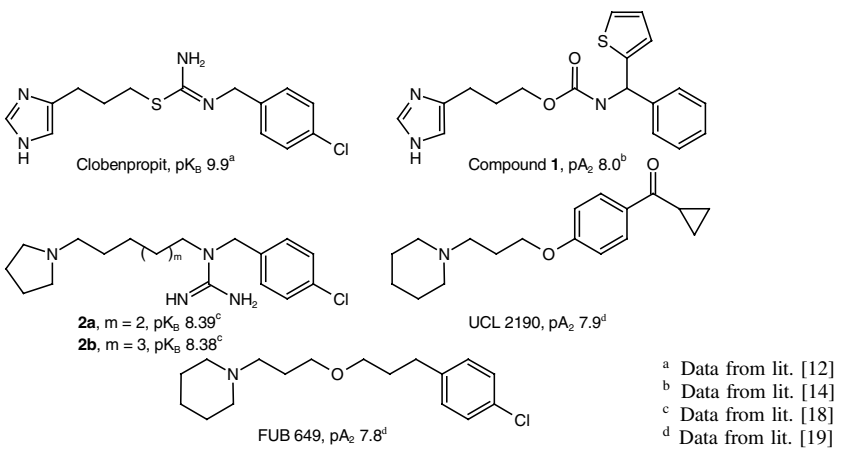
1. Introduction

The histamine H_3 receptor, which was first described by Arrang et al. in 1983 [1], belongs to the superfamily of G-protein-coupled receptors. Recently, the human H_3 receptor [2] was cloned followed thereafter by cloning of the receptors in rat [3, 4] and in guinea-pig [5]. These findings and the detection of a new member of the histamine receptor class, the histamine H_4 receptor [6], brought new impetus to this field of research.

It is known that histamine H_3 receptors act not only as autoreceptors, modulating the synthesis and release of histamine in and from cerebral neurones [7, 8], but they also act as heteroreceptors – playing an important role in the release of the respective neurotransmitters [for review see 9, 10]. The majority of potent histamine H_3 receptor ligands are derived from histamine itself and contain an imidazole moiety monosubstituted in the 4-position [9, 10]. In functional tests these compounds demonstrate agonist, partial agonist, neutral antagonist, or inverse agonist activity. Histamine H_3 receptor antagonists blocking the auto- and heteroreceptors can be potential drugs for the treatment of various diseases or pathophysiological conditions of the central nervous system (CNS) e.g., dementia, epilepsy, narcolepsy, or schizophrenia [9, 10]. During the last years a large number of histamine H_3 receptor antagonists have been synthesised [for review see 9, 10 and 11]. One compound with high *in vitro* potency is clobenpropit with an isothiourea group [12]. However it was not introduced into clinical trials most probably because of its hepatotoxicity, which may be caused by the isothiourea structure. In the search for therapeutically more useful compounds a lot of structures with different functionalities have been obtained serving as bioisosteres for the isothiourea group, e.g., carbamates [13].

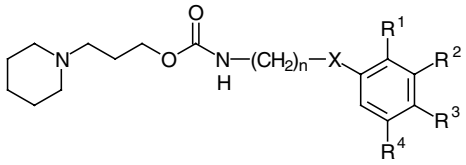
Recent results on carbamate derivatives of 3-(1*H*-imidazol-4-yl)-propanol have been shown to be H_3 receptor antagonists with high affinity *in vitro* and high potency *in vivo* [13–16], e.g., compound **1**. However, as the imidazole moiety is known to cause interactions with cytochrome P450 (CYP450) [17 and the references cited therein], they may be of limited therapeutic value. Therefore, the need for non-imidazole H_3 ligands has been recognised. Very recently non-imidazole *N*-heterocyclic compounds have been synthesised, e.g., compounds **2a, b** as well as the piperidine analogues of ciproxifan (UCL 2190) or FUB 181 (FUB 649) [18, 19].

This work is a continuation of our previous study [20]. We are looking for non-imidazole histamine H_3 receptor antagonists as carbamate derivatives of 3-piperidino-1-propanol. Our starting point, based on the literature [19] and patent [21] study, was the observation that ether derivatives of 3-piperidino-1-propanol showed moderate to good H_3 receptor antagonist activity. The aim of the present



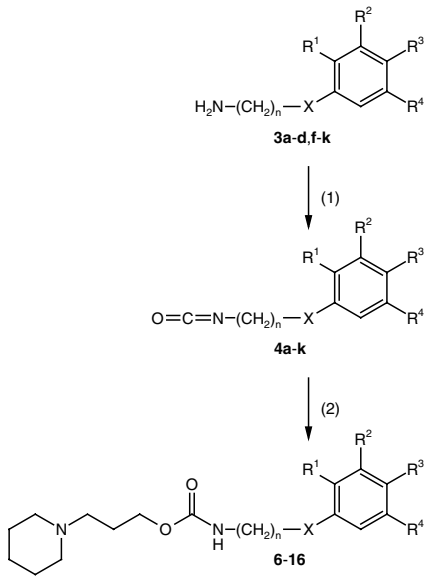
[a] Data from lit. [12]
[b] Data from lit. [14]
[c] Data from lit. [18]
[d] Data from lit. [19]

Table 1: Structures and physicochemical data of compounds 6–16



Compd.	n	X	R^1	R^2	R^3	R^4	Formula (molecular weight)	M.p. (°C)	Yield (%)
6	0	–	OCH_3	H	H	H	$C_{16}H_{26}N_2O_3 \cdot C_2H_2O_4$ (382.4)	163–165	80
6a	0	–	H	H	H	H	Lit. [19]		
7	0	–	H	OCH_3	H	H	$C_{16}H_{26}N_2O_3 \cdot C_2H_2O_4 \cdot 0.25\ H_2O$ (386.9)	130–132	42
8	0	–	H	H	OCH_3	H	$C_{16}H_{26}N_2O_3 \cdot C_2H_2O_4$ (382.4)	141–144	60
9	0	–	H	OCH_3	H	OCH_3	$C_{17}H_{26}N_2O_4 \cdot C_2H_2O_4$ (412.4)	150	57
10	0	–	H	OCH_3	OCH_3	OCH_3	$C_{18}H_{28}N_2O_5 \cdot C_2H_2O_4$ (442.5	141–144	46
11	0	–	H	H	OC_2H_5	H	$C_{17}H_{26}N_2O_3$ (306.4)	134–135	63
12	0	–	H	H	OC_5H_{11}	H	$C_{20}H_{32}N_2O_3 \cdot C_2H_2O_4$ (438.5)	142	20
13	0	–	H	H	OC_6H_5	H	$C_{21}H_{26}N_2O_3 \cdot C_2H_2O_4 \cdot 0.2\ H_2O$ (448.1)	146–148	39
14	2	–	H	H	OCH_3	H	$C_{18}H_{28}N_2O_3 \cdot C_2H_2O_4 \cdot 0.2\ H_2O$ (414.1)	62–68	17
14a	2	–	H	H	H	H	Lit. [20]		
15	2	O	H	H	H	H	$C_{17}H_{26}N_2O_3 \cdot C_2H_2O_4$ (396.5)	154–158	38
15a	3	–	H	H	H	H	Lit. [20]		
16	2	O	H	H	OCH_3	H	$C_{18}H_{28}N_2O_4 \cdot C_2H_2O_4 \cdot 0.25\ H_2O$ (431.0)	121–124	59

Scheme 1



5: 3-piperidino1-propanol; n = 0,2; X = –, O; R^1, R^2, R^4 = H, OCH_3; R^3 = H, OCH_3, OC_2H_5, OC_5H_{11}, OC_6H_5.

(1) diphosgene or triphosgene, AcOEt; (2) **5**, MeCN, reflux.

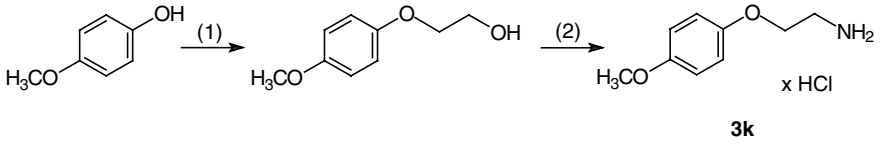
work was the synthesis and pharmacological *in vitro* evaluation of new carbamates with an additional ether moiety. We have prepared eleven carbamates with alkoxy (mostly methoxy) groups (Table 1). These compounds were tested on guinea-pig ileum strips for H_3 potency [22] and also for selectivity reasons on histamine H_1, H_2, and muscarinic M_3 receptors in functional tests on isolated organs of guinea-pig [23, 24].

2. Investigations, results and discussion

2.1. Chemistry

The key synthetic intermediate of all H_3 receptor antagonists of the new series was 3-piperidino-1-propanol (**5**). It was obtained by alkylation of piperidine with 3-bromo-1-propanol in acetronitrile in the presence of potassium carbonate according to the literature [25]. Carbamates **6**–**16** were prepared by the reaction of **5** with the appropriate isocyanates **4a**–**k** (Scheme 1). Isocyanates which were not commercially available (**4a**–**d**, **f**–**k**), were obtained from the corresponding amines **3a**–**d**, **f**–**k** by reaction with excess trichloromethyl chloroformate (diphosgene) or bis(trichloromethyl) carbonate (triphosgene) [26, 27]. 2-[4-(Methoxy)phenoxy]ethylamine (**3k**) was synthesized from 2-[4-(methoxy)phenoxy]ethanol by a Mitsunobu-type reaction [28] (Scheme 2). 2-(4-(Methoxy)phenoxy)ethanol was prepared by refluxing 4-methoxyphenol in sodium methanolate with 2-bromoethanol (Scheme 2). Compounds **6**–**16**

Scheme 2



(1) Br-$(CH_2)_2$–OH, MeONa/MeOH; (2) i: diethyl azodicarboxylate (DEAD), phthalimide, Ph_3P, THF; ii: H_2NNH_2, EtOH; iii: HCl, EtOH.

were purified by means of column chromatography (CC) and characterised as salts of oxalic acid (**6**–**10**, **12**–**16**) or as a free base (**11**). Structures, some physicochemical data, and purification conditions of final compounds are given in Tables 1 and 2. All compounds gave satisfactory analytical results (^{1}H NMR, MS, IR, CHN).

2.2. Pharmacological results and discussion

The novel compounds **6**–**16** (Table 1) were tested *in vitro* for potential antagonism at peripheral histamine H_3 receptors. 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 myenteric plexus) in the presence of the antagonist according to our previous experience [20]. In order to avoid a mimicking effect of histamine H_3 receptor blockade by interaction with muscarinic M_3 receptors, the compounds were routinely checked for M_3 receptor affinity expressed as pA_2 (M_3) value (Table 3). The potential H_3-receptor antagonists investigated were tested at concentrations that did not block M_3 receptors (concentration used for H_3 receptor assay $\leq 0.5 \cdot 10^{-pA_2}$ (M_3)).

Table 2: Preparative and analytical data of compounds 6–16

Compd.	Solvent CC	IR (C=O) (cm^{-1})	MS m/e (rel. int. in%)	^{1}H NMR (δ in ppm)
6	CH_2Cl_2 : MeOH : MeOH saturated with NH_3 98 : 2 : 1	1730 s	292 (9[M]$^{+\cdot}$), 98 (100)	[DMSO-d_6] 8.39 s, 1 H, CO−N*H**; 7.66 d, J = 7.5 Hz, 1 H, Ph-6-H; 7.10–6.98 m, 2 H, Ph-3,5-H; 6.91 t, J = 7.5 Hz, Ph-4-H; 4.11 t, J = 6.1 Hz, 2 H, C*H*$_2$−O; 3.80 s, 3 H, O−C*H*$_3$; 3.18–2.97 m, 6 H, pip-2,6-H + pip-C*H*$_2$; 2.01 def qu, 2 H, pip-CH$_2$−C*H*$_2$; 1.79–1.65 m, 4 H, pip-3,5-H; 1.52 br, 2 H, pip-4-H
7	$CHCl_3$: MeOH : MeOH saturated with NH_3 95 : 5 : 2	1730 s	292 (6[M]$^{+\cdot}$), 98 (100)	[DMSO-d_6] 9.66 s, 1 H, CO−N*H**; 7.17 t, J = 8.2 Hz, 1 H, Ph-5-H; 7.13 s, 1 H, Ph-2-H; 7.01 d, J = 7.9 Hz, 1 H, Ph-4-H; 6.58 dd, J = 2.3 Hz, J = 6.0 Hz, 1 H, Ph-6-H; 4.13 t, J = 6.2 Hz, 2 H, C*H*$_2$−O; 3.71 s, 3 H, O−C*H*$_3$; 3.06–3.02 m, 6 H, pip-2,6-H + pip-C*H*$_2$; 2.02 qu, J = 7.4 Hz, 2 H, pip-CH$_2$−C*H*$_2$; 1.73–1.70 m, 4 H, pip-3,5-H; 1.52 br, 2 H, pip-4-H
8	CH_2Cl_2 : MeOH : MeOH saturated with NH_3 99 : 1 : 1	1723 s	292 (10[M]$^{+\cdot}$), 98 (100)	[DMSO-d_6] 9.46 s, 1 H, CO−N*H**, 7.35 d, J = 8.4 Hz, 2 H, Ph-2,6-H; 6.86 dd, J = 8.61 Hz, J = 1.90 Hz, 2 H, Ph-3,5-H; 4.11 t, J = 6.3 Hz, 2 H, C*H*$_2$−O; 3.70 s, 3 H, O−C*H*$_3$; 3.19–2.99 m, 6 H, pip-2,6-H + pip-C*H*$_2$; 2.02 qu, J = 7.7 Hz, 2 H, pip-CH$_2$−C*H*$_2$; 1.79–1.63 m, 4 H, pip-3,5-H; 1.52 br, 2 H, pip-4-H
9	$CHCl_3$: MeOH : MeOH saturated with NH_3 95 : 5 : 1	1736 s	322 (9[M]$^{+\cdot}$), 98 (100)	[DMSO-d_6] 9.65 s, 1 H, CO−N*H**; 6.71 d, J = 2.1 Hz, 2 H, Ph-2,6-H; 6.16 t, J = 2.2 Hz, 1 H, Ph-4-H; 4.12 t, J = 6.3 Hz, 2 H, C*H*$_2$−O; 3.69 s, 6 H, 2 · O−C*H*$_3$; 3.20–2.94 m, 6 H, pip-2,6-H + pip-C*H*$_2$; 2.02 qu, J = 7.7 Hz, 2 H, pip-CH$_2$−C*H*$_2$; 1.81–1.62 m, 4 H, pip-3,5-H; 1.52 br, 2 H, pip-4-H
10	$CHCl_3$: MeOH : MeOH saturated with NH_3 95 : 5 : 1	1729 s	352 (7[M]$^{+\cdot}$), 98 (100)	[DMSO-d_6] 9.57 s, 1 H, CO−N*H**; 6.84 s, 2 H, Ph-2,6-H; 4.12 t, J = 6.2 Hz, C*H*$_2$−O; 3.72 s, 9 H, 3 · O−C*H*$_3$; 3.06–3.01 m, 6 H, pip-2,6-H + pip-C*H*$_2$; 2.01 def qu, 2 H, pip-CH$_2$−C*H*$_2$; 1.84–1.64 m, 4 H, pip-3,5-H; 1.55 br, 2 H, pip-4-H
11	–	1723 s	306 (9[M]$^{+\cdot}$), 98 (100)	[$CDCl_3$] 7.29–7.20 m, 2 H, Ph-3,5-H; 6.87–6.80 m, 2 H, Ph-2,6-H; 6.70 s, 1 H, CO−N*H**; 4.21 t, J = 6.3 Hz, 2 H, C*H*$_2$−O; 4.04–3.97 q, J = 7.0 Hz, 2 H, O−C*H*$_2$−CH$_3$; 2.80–2.48 m, 6 H, pip-2,6-H + pip-C*H*$_2$; 2.05 qu, J = 6.3 Hz, 2 H, pip-CH$_2$−C*H*$_2$; 1.90–1.70 m, 4 H, pip-3,5-H; 1.52 br, 2 H, pip-4-H; 1.40 t, J = 7.0 Hz, 3 H, C*H*$_3$
12	$CHCl_3$: MeOH : MeOH saturated with NH_3 98 : 2 : 1	1732 s	348 (5[M]$^{+\cdot}$), 98 (100)	[DMSO-d_6] 9.43 s, 1 H, CO−N*H**; 7.33 d, J = 8.3 Hz, 2 H, Ph-2,6-H; 6.85 d, J = 9.0 Hz, 2 H, Ph-3,5-H; 4.11 t, J = 6.3 Hz, 2 H, C*H*$_2$−O; 3.89 t, J = 6.5 Hz, 2 H, O−C*H*$_2$; 3.04–3.00 m, 6 H, pip-2,6-H + pip-C*H*$_2$; 1.99 qu, J = 6.5 Hz, 2 H, pip-CH$_2$−C*H*$_2$; 1.70–1.65 m, 6 H, pip-3,5-H + O−CH$_2$−C*H*$_2$; 1.52 br, 2 H, pip-4-H; 1.44–1.26 m, 4 H, (C*H*$_2$)$_4$−CH$_3$; 0.89 t, J = 7.1 Hz, 3 H, C*H*$_3$
13	$CHCl_3$: MeOH : MeOH saturated with NH_3 97 : 3 : 1	1727 s	354 (6[M]$^{+\cdot}$), 98 (100)	[DMSO-d_6] 9.81 s, 1 H, CO−N*H**, 7.47 d, J = 8.7 Hz, 2 H, Ph-2,6-H; 7.40–7.29 m, 2 H, Ph-3,5-H; 7.09 t, J = 7.4 Hz, Ph-4′-H; 7.02–6.89 m, 4 H, Ph-2′,3′,5′,6′-H; 4.14 t, J = 6.3 Hz, 2 H, C*H*$_2$−O; 3.24–2.87 m, 6 H, pip-2,6-H + pip-C*H*$_2$; 2.02 qu, J = 7.6 Hz, 2 H, pip-CH$_2$−C*H*$_2$; 1.81–1.62 m, 4 H, pip-3,5-H; 1.52 br, 2 H, pip-4-H
14	CH_2Cl_2 : MeOH : MeOH saturated with NH_3 96 : 4 : 1.5	1713 s	320 (4[M]$^{+\cdot}$), 98 (100)	[DMSO−d_6] 7.17 def t, 1 H, CO−N*H**; 7.13–7.07 m, 2 H, Ph-3,5-H; 6.87–6.82 m, 2 H, Ph-2,6-H; 3.98 t, J = 6.3 Hz, 2 H, C*H*$_2$−O; 3.72 s, 3 H, O−C*H*$_3$; 3.19–2.97 m, 8 H, pip-2,6-H + pip-C*H*$_2$ + CONH−C*H*$_2$; 2.64 t, J = 7.1 Hz, 2 H, C*H*$_2$-Ph; 1.92 def qu, 2 H, pip-CH$_2$−C*H*$_2$; 1.75–1.65 m, 4 H, pip-3,5-H; 1.50–1.40 m, 2 H, pip-4-H
15	CH_2Cl_2 : MeOH : MeOH saturated with NH_3 93 : 7 : 6 drops per 100 ml	1720 s	306 (3[M]$^{+\cdot}$), 98 (100)	[DMSO-d_6] 7.37 t, J = 5.3 Hz, CO−N*H**; 7.32–7.24 m, 2 H, Ph-3,5-H; 6.99–6.85 m, 3 H, Ph-2,4,6-H; 4.06–3.92 m, 4 H, C*H*$_2$−O + C*H*$_2$−O−Ph; 3.39–3.29 q, J = 5.7 Hz, 2 H, CONH−C*H*$_2$; 3.14–2.86 m, 6 H, pip-2,6-H + pip-C*H*$_2$; 1.93 qu, J = 6.8 Hz, 2 H, pip-CH$_2$−C*H*$_2$; 1.81–1.58 m, 4 H, pip-3,5-H; 1.51 br, 2 H, pip-4-H
16	$CHCl_3$: MeOH : MeOH saturated with NH_3 100 : 2 : 2	1721 s	336 (8[M]$^{+\cdot}$), 98 (100)	[DMSO-d_6] 7.35 s, 1 H, CO−N*H**; 6.89–6.79 m, 4 H, Ph-2,3,5,6-H; 4.01 t, J = 6.0 Hz, 2 H, C*H*$_2$−O; 3.91 t, J = 5.5 Hz, 2 H, −C*H*$_2$−O−Ph; 3.69 s, 3 H, O−C*H*$_3$; 3.38–3.26 q, J = 5.6 Hz, 2 H, CONH−C*H*$_2$; 3.25–2.88 m, 6 H, pip-2,6-H + pip-C*H*$_2$; 1.93 def qu, 2 H, pip-CH$_2$−C*H*$_2$; 1.75–1.61 m, 4 H, pip-3,5-H; 1.51 br, 2 H, pip-4-H

Table 3: Structures and antagonist activity of compounds 6–16 and 6a, 14a, 15a at histamine H_1, H_2, H_3, and muscarinic M_3 receptors

Compd.	H_1 [a] $pA_2 \pm$ SEM	H_2 [b] $pD_{2'} \pm$ SEM[c]	H_3 [c] pA_2 (95% conf. limit)	M_3 [d] $pA_2 \pm$ SEM
6	4.89 ± 0.04	4.66 ± 0.05	6.11 (5.96–6.23)	4.69 ± 0.03
6a [e]	4.95 ± 0.03	4.69 ± 0.03	6.18 (5.89–6.47)	4.70
7	5.63 ± 0.03	4.66 ± 0.02	6.18 (5.99–6.34)	4.95 ± 0.07
8	5.35 ± 0.01	4.59 ± 0.04	6.76 (6.56–6.96)	4.54 ± 0.02
9	5.96 ± 0.03	5.54 ± 0.14	6.28 (5.98–6.49)	5.85 ± 0.10
10	4.83 ± 0.05	4.25 ± 0.16	6.52 (6.30–6.74)	4.62 ± 0.02
11	5.24 ± 0.02	4.78 ± 0.26	6.58 (6.50–6.66)	4.61 ± 0.14
12	6.31 ± 0.06	5.01 ± 0.22	6.66 (6.52–6.78)	5.78 ± 0.07
13	6.35 ± 0.06	5.41 ± 0.18	6.68 (6.41–6.92)	5.82 ± 0.12
14	4.97 ± 0.03	5.03 ± 0.33	6.38 (6.19–6.57)	4.63 ± 0.06
14a [f]	4.78 ± 0.05	5.38 ± 0.15	5.75 (5.34–6.06)	4.64 ± 0.06
15	4.96 ± 0.07	4.70	6.25 (6.09–6.41)	4.53 ± 0.06
15a [f]	5.15 ± 0.03	4.56 ± 0.33	6.28 (6.22–6.34)	4.85 ± 0.03
16	5.46 ± 0.03	nt [g]	6.21 (6.16–6.26)	4.37 ± 0.05

[a] H_1 receptor assay on guinea-pig ileum [23]; [b] H_2 receptor assay on guinea-pig atrium [24]; [c] H_3 receptor assay on guinea-pig ileum [24]; [d] M_3 receptor assay on guinea-pig ileum [23]; [e] [19], Schunack et al. unpublished results; [f] [20]; [g] nt, not tested.

The results for 3-piperidino-1-propanol-derived carbamates **6**–**16**, containing an additional ether functionality placed differently, are presented in Table 3. For comparison the previously described carbamates without ether moieties **6a**, **14a**, and **15a** were also included (for structures see Table 1). All compounds investigated possess measurable albeit moderate affinity for histamine H_3 receptors of the guinea-pig (pA_2 6.11–6.76).

It must be stated that most compounds were active in a similar concentration range and that the structural changes performed induced only small changes in activity. Despite the level of statistical significance we want to show some trends in structure-activity relationship. Interestingly introduction of ether groups in different position of the phenyl group differently influenced activity in comparison to the related compounds without this functionality. Contrary to an almost missing effect of a methoxy substitent in *ortho*- (**6**) or *meta*- (**7**) position, a methoxy group placed in *para*-position caused a slight increase in activity allowing to obtain the most active compound in this series (**8**). A similar apparent beneficial effect was observed for the pair of compounds with the longer spacer (with two carbons) (**14a** without $<$**14** with methoxy group), but not more for the alkyl aryl ethers with longer spacers (3 units) (**15**, **16**). Additional methoxy groups introduced in the 3,5-positions (**9**) had only a slightly positive effect in comparison to **7** with only one methoxy group, similarly to triple substitution in the 3,4,5-position (**10**). The more bulky substituents at the *para*-position (**11**, **12**, **13**) were well tolerated. An ether function placed in the spacer has shown bioisosteric properties (compare **15a** and **15**).

The ether functionality had also some impact on the selectivity versus M_3, H_1 and H_2 receptors (Table 3). The selectivity for M_3 receptors which is fairly good for almost all compounds dropped obviously in the case of compounds **9**, **12**, and **13**. All compounds investigated behaved as weak antagonists for histamine H_1 as well as for H_2 receptors. Compounds **7**, **9**, **12**, **13**, and **14a** showed less than one order of magnitude difference in affinity for the other receptor tested in comparison to their affinity for H_3 receptors.

3. Experimental

3.1. Chemistry

Melting points were determined on a Mel-Temp II apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker DPX 400 Avance (400 MHz) spectrometer. Chemical shifts are expressed in ppm downfield from internal Me_4Si as reference. ^{1}H NMR data are reported in the following order: multiplicity (br, broad; def, deformed; s, singlet; d, dublet; dd, doublet of doublets; t, triplet; q, quartet; qu, quintet; m, multiplet); approximate coupling constants J in Hertz; number of protons; *, exchangeable by D_2O; Pip, piperidine; Ph, phenyl. MS were obtained on an EI-MS Finnigan MAT CH7A (70 eV, 170°). IR spectra were recorded with a Perkin-Elmer 1420 Ratio-Recording or a Perkin-Elmer 297 spectral photometer from KBr discs (s, strong). Elemental analyses (C, H, N) were measured on a Perkin-Elmer 240 B or a Perkin-Elmer 240 C instrument and were within ±0.4% of theoretical values for all final compounds. CC was performed using silica gel 60 (0.063–0.20 mm; Merck). TLC was carried out using silica gel F_{254} plates (Merck). The spots were visualized with Dragendorff's reagent or by UV absorption at 254 nm.

3.1.1. Starting materials: 3-Piperidino-1-propanol **5** *and 2-[4-(methoxy)phenoxy]ethanamine* (**3k**)

3-Piperidino-1-propanol was obtained as described in [20, 25]; b.p. 110–130 °C$_{100-120\ mm\ Hg}$ (b.p. 125 °C$_{30\ mm\ Hg}$ [25]), yield 76%.

Synthesis of 2-[4-methoxyphenoxy]ethanol: To a solution of 4-(methoxy)-phenol (0.5 mol; 6.4 g) in 30 ml of MeONa was added dropwise 2-bromo-1-ethanol (0.5 mol; 3.5 ml) and heated to reflux for 2 h. The solution was cooled, NaBr filtered off, and the filtrate was evaporated under reduced pressure. Water was added to the oily residue, and the precipitate was dissolved in CH_2Cl_2 and washed with NaOH (20%) to yield 5.1 g (68%) of white powder [29] (m.p. 65 °C).

Compound **3k** was prepared from 2-(4-(methoxy)phenoxy)ethanol in a Mitsunobu protocol-adapted Gabriel synthesis [28]. The corresponding *N*-alkylphthalimide (m.p. 130–132 °C; lit. [30] 128–129 °C) was transferred into the desired amine by hydrazinolysis as described earlier [13]. **3k** was isolated as hydrochloride from ethanol as white powder (m.p. 220 °C (224–226 °C [31]); ^{1}H NMR (DMSO-d_6): $\delta = 8.30$ (br, 3 H, NH_3^+), 7.84–6.92 (m, 4 H, Ph-2,3,5,6-H), 4.10 (t, J = 5.2 Hz, 2 H, Ph−O−CH_2), 3.68 (s, 3 H, OCH_3), 3.10–3.16 (q, J = 5.2 Hz, 2 H, $NH_3^+-CH_2$).

3.1.2. Synthesis of carbamates **6–9, 11–16**

General procedure*:* A solution of trichloromethyl chloroformate (0.37 ml, 3 mmol) or bis(trichloromethyl) carbonate (0.89 g, 3 mmol) and a catalytic amount of charcoal in 20 ml of dry ethyl acetate were mixed at room temperature for 15 min. After heating up to 50 °C, the appropriate amine **3** (2.5 mmol) in 15 ml of dry ethyl acetate was rapidly added. The reaction mixture was heated to reflux for 5 h. Then the black solution was cooled, filtered, and the solvent was evaporated under reduced pressure. The freshly prepared isocyanate was redissolved in 30 ml of dry MeCN, and 3-piperidino-1-propanol (**5**) (2.5 mmol, 0.36 g) in 15 ml of dry MeCN was added. The solution was refluxed for 5–18 h (controlled by TLC) and concentrated in vacuo (**6**–**9**, **12**–**16**). The residue was purified by CC. The pure fractions were concentrated in vacuo, dried and the carbamates were crystallized as salts of oxalic acid from EtOH/Et_2O (**6**–**9**, **12**–**16**). Carbamate **11** (free base) precipitated from the solution as solid. It was recrystallized from MeCN.

3.1.3. Synthesis of carbamate **10**

3,4,5-Trimethoxyphenyl isocyanate (**4e**) (2.5 mmol, 0.52 g) was rapidly added to a solution of 3-piperidino-1-propanol **5** (2.5 mmol, 0.36 g) in

30 ml of dry MeCN and heated to reflux for 3.5 h. After concentration in vacuo the residue was purified by CC. The pure fractions were concentrated in vacuo, dried and crystallized as salts of oxalic acid from EtOH/Et_2O.

3.2. Pharmacology

3.2.1. Histamine H_3 receptor antagonist assay on guinea-pig ileum

Antagonist histamine H_3 receptor activity was measured by the concentration-dependent inhibition of electrically evoked twitches of longitudinal muscle strips of guinea-pig ileum induced by (*R*)-α-methylhistamine in the presence of the antagonist by at least five experiments [22]. All compounds showed weak to moderate H_3 receptor antagonist activity. The potency of an antagonist was reflected by the apparent pA_2 values [32]. Full pA_2 values were calculated according to the Schild regression analysis [33]. All details were described earlier [20].

3.2.2. Histamine H_1, H_2, and muscarinic M_3 receptor assays on isolated organs of guinea-pig

To investigate the receptor selectivities of the compounds, functional *in vitro* tests were performed on guinea-pig ileum for H_1 and M_3 receptor activites and on the spontaneously beating right atrium for H_2 receptor activity according to standard procedures described by Hirschfeld et al. and Ligneau et al. [23, 24]. Results are expressed as mean ± standard error (SEM or SE) unless otherwise indicated. The number of experiments were 4–12 for H_1 and M_3 and at least 2 for H_2 receptor assays.

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