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Substituted *N*-phenylcarbamates as histamine H_3 receptor antagonists with improved *in vivo* potency

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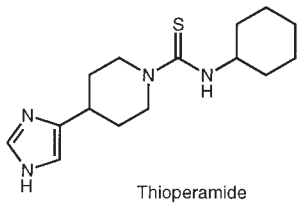
Novel substituted *N*-phenylcarbamates as derivatives of 3-(1*H*-imidazol-4-yl)propanol were prepared and tested for their antagonist potency *in vitro* and *in vivo* at histamine H_3 receptors. Structural modifications with different alkyl and acetyl moieties were performed in an attempt to optimize pharmacodynamic and pharmacokinetic effects. Most compounds are active in a functional test for histamine H_3 receptors on rat cerebral cortex synaptosomes as well as in a peripheral model on guinea pig ileum. But only carbamates without too bulky lipophilic residues showed pronounced to high antagonist potency on the enhancement of endogenous histamine in brain after p.o. administration to mice (ED_{50} values of 5.5 to 0.86 $mg \cdot kg^{-1}$). The tested compounds presented weak activities at histamine H_1, H_2, and muscarinic M_3 receptors thus demonstrating their H_3-receptor selectivity.

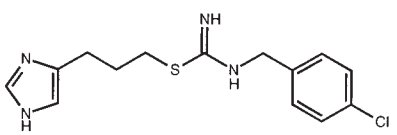
1. Introduction

The third histamine receptor subtype was identified by Arrang et al. [1] as an autoreceptor on histaminergic neurons regulating histamine synthesis in and release from cerebral neurons in an inhibitory way [2, 3]. Meanwhile it is known that H_3 receptors also occur on nonhistaminergic nerve endings modulating the release of different neurotransmitters, e.g., from dopaminergic [4], serotonergic [5], noradrenergic [6, 7], and peptidergic neurons [8]. The highest density of histamine H_3 receptors was found in the brain [9], but H_3 receptors were identified as well in peripheral tissues of different species. Blockade of auto- and heteroreceptors by H_3-receptor antagonists appears to be a promising approach for potential drugs for the treatment of different diseases or conditions of the CNS like epilepsy [10], stress [11], memory and learning deficits [12–14], schizophrenia [15], arousal and sleep disorders [16, 17], and Alzheimer's disease [18]. Several histamine H_3-receptor antagonists showing structural diversity are known with thioperamide [9] and clobenpropit [19] as reference compounds. Thioperamide was the first selective histamine H_3-receptor antagonist with high *in vitro* and *in vivo* potency [9], and therefore, is the prototypic antagonist for this receptor system. Later, clobenpropit was discovered showing even higher *in vitro* activity, but clearly less activity than thioperamide under *in vivo* conditions [19]. None of these two compounds were introduced into clinical trials most likely because of unwanted side-effects like hepatotoxicity, presumably depending on the thiourea or the isothiourea moieties. Therefore, histamine H_3 receptor antagonists without sulfur-containing functionalities have been developed to avoid toxicity problems, e.g., carbamates [20].

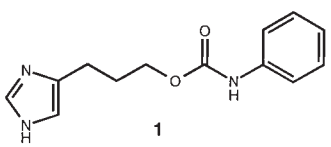
The *N*-phenylcarbamate **1** was equipotent to thioperamide *in vivo* and was therefore taken as a lead for further development. Alkyl and acetyl substituents in various positions were introduced in **1** (Table 1) in search for nontoxic, centrally acting, highly potent, and selective H_3-receptor antagonists. The histamine H_3-receptor activities of all compounds were investigated in an *in vitro* [^{3}H]histamine-release assay using synaptosomes of rat cerebral cortex [21] and additionally in an *in vivo* test evaluating the effect on the N^{τ}-methylhistamine level after p.o. administration to Swiss mice [21]. Furthermore, selected compounds were also tested for antagonist activity in another functional H_3-receptor test on guinea pig ileum strips [22]. Moreover, the activities for selected carbamates at histamine H_1, H_2, and muscarinic M_3 receptors were screened in functional tests on isolated organs of the guinea pig [23, 24].



Thioperamide



Clobenpropit



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2. Investigations, results and discussion

2.1. Chemistry

Carbamates are prepared by standard methods adding an appropriate isocyanate to an alcohol. 3-(1 *H*-Imidazol-4-yl)propanol · HCl [25] (**a**, Scheme) was obtained in five steps starting with urocanic acid by esterification, hydrogenation on Pd/C [26], tritylation, reduction with complex hydrides, and subsequent acidic cleavage of the protecting group [25]. The required isocyanates for the carbamates **1**–**6** and **9**–**11** (Table 1) were synthesized refluxing the corresponding amines with excess diphosgene [27], a liquid phosgene substitute (Scheme, A). Excess diphosgene was distilled, and remaining isocyanates were immediately added to compound **a**. This alcohol was used in form of its salt because protonation of the imidazole ring avoids its attack by isocyanates and reduces by-products.
Isocyanates for compounds **7** and **8** (Table 1) were prepared in a modified Curtius reaction [28, 29] starting from the corresponding carboxylic acid which reacted with diphenylphosphorazidate (DPPA) and triethylamine (TEA). This mixture was refluxed for 30 min getting the intermediate isocyanates, and then in a one-pot procedure alcohol **a** (Scheme) was added.
All compounds were chromatographically purified, characterized as salts of maleic acid (**1**, **2**, **4**–**6**, **10**, **11**) or oxalic acid (**3**, **7**–**9**), and gave satisfactory analytical results (NMR, MS, CHN). Yields and m.p. of the designed compounds are given in Table 1. ^{1}H NMR and MS spectra are presented only for selected compounds in the Experimental part.

2.2. Pharmacological results and discussion

2.2.1. Histamine H_3-receptor in vitro testing on synaptosomes of rat cerebral cortex

The novel compounds were tested for their effect at histamine H_3 receptors *in vitro* on synaptosomes of rat cerebral cortex (Table 1). All compounds had antagonist properties at histamine H_3 receptors. Effects of substituents with electron-releasing and electron-withdrawing properties were investigated. Introduction of one methyl group (**2**, **3**, **4**) led to potent histamine H_3-receptor antagonists. Although the position of the substituent in the ring system seemed to be of minor influence, a slight preference without significance was found for the *para*-position. When the volume of the substituent was increased (**5**) or an additional methyl group (**6**) was introduced the activity of the compounds was decreased compared to **1**. Carbamates with rather bulky lipophilic residues (**7**, **8**) were clearly less potent *in vitro* than **1**. Thus it can be speculated that substituents decrease activity when they are too bulky although the number of compounds seems to be too small for a general conclusion. Despite the missing potency of **7** electron-withdrawing substituents like the acetyl moiety in **10** were also tolerated. Most other compounds were more or less active in a comparable nanomolar concentration range. In a previous investigation [11] a large variety of substituents with different electronic properties were introduced maintaining H_3-receptor affinity. Therefore, the loss in *in vitro* activity with compounds **7** and **8** is the most surprising *in vitro* result.

2.2.2. Histamine H_3-receptor in vivo testing in mice brain after p.o. administration.

Additionally all newly synthesized carbamates were tested for their effects at histamine H_3 receptors under *in vivo* conditions on mice after p.o. administration (Table 1). In agreement with the *in vitro* testing all compounds showed antagonist *in vivo* properties at H_3 receptors. Introduction of a methyl group (**2**–**4**) did not improve potency compared to **1** when tested under *in vivo* conditions. No strong influence of the substitution pattern, comparable to the data of the *in vitro* test system, could be detected. An increase in lipophilicity (**5**, **6** vs. **2**, **3**, **4**) led to compounds which were equipotent to **1** and to thioperamide. The *in vivo* values present the sum of pharmacodynamic and pharmacokinetic processes of the compounds administered, while under *in vitro* conditions results depend more on ligand/receptor-interaction. Thus, compounds **1**, **5**, and **6** appeared to possess improved pharmacokinetic properties in comparison to the rest of the carbamate derivatives of this series. When the lipophilic residue became too bulky or was electron-withdrawing, however, no *in vivo* activity could be detected (**7**–**11**).
Compounds **1**, **2**, **5**, and **6** were in the same potency range *in vivo* as the reference compound thioperamide. Especially compound **6** showed pharmacokinetic improvement compared to formerly known carbamate derivatives [20]. It can be speculated that by changing the substituents or the substitution pattern different pharmacodynamic properties could be designed for the novel compounds by maintaining H_3-receptor antagonist potency.

2.2.3. Screening of compounds at related receptors and test systems

Compounds **3**–**11** were additionally screened for their activities at a peripheral histamine H_3 receptor, at histamine

Scheme

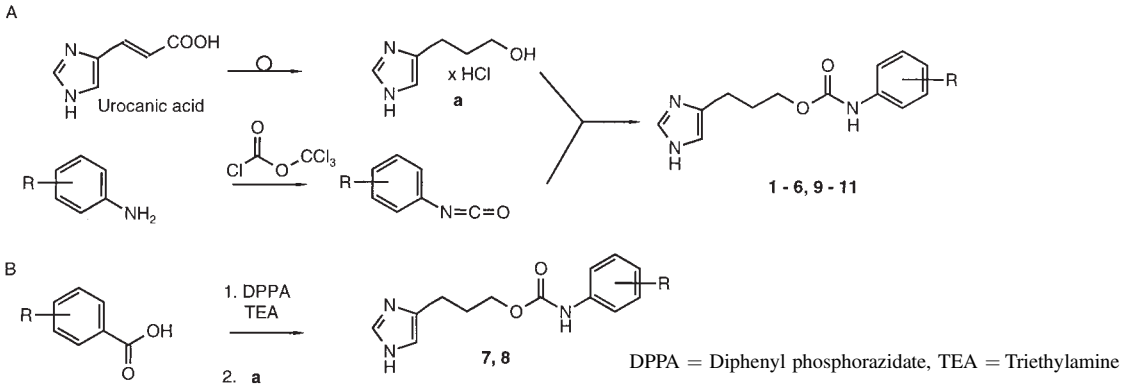
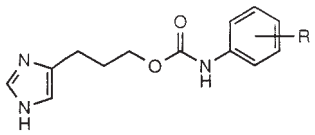


Table 1: Histamine H_3-receptor antagonist potencies *in vitro* and *in vivo* for compounds 1–11



Compd.	R	Formula	M_r	Yield (%)	M.p. (°C)	*in vitro* K_i (nM)	*in vivo* ED_{50} (mg kg^{-1}) p.o.
1[a]	H	$C_{13}H_{15}N_3O_2 \cdot C_4H_4O_4 \cdot 0.25\,H_2O$	365.9	89	115	14 ± 8	1.3 ± 0.6
2[a]	4-CH_3	$C_{14}H_{17}N_3O_2 \cdot C_4H_4O_4 \cdot 0.25\,H_2O$	379.9	97	142	11 ± 6	2.1 ± 0.9
3	3-CH_3	$C_{14}H_{17}N_3O_2 \cdot C_2H_2O_4$	349.3	80	142	19 ± 7	3.2 ± 1.3
4	2-CH_3	$C_{14}H_{17}N_3O_2 \cdot C_4H_4O_4$	375.4	63	100	79 ± 30	5.5 ± 1.6
5	2-C_2H_5	$C_{15}H_{19}N_3O_2 \cdot C_4H_4O_4 \cdot 0.25\,H_2O$	393.9	31	123	39 ± 13	1.4 ± 0.4
6	3,5-$(CH_3)_2$	$C_{15}H_{19}N_3O_2 \cdot C_4H_4O_4 \cdot 0.25H_2O$	393.9	42	108	44 ± 13	0.83 ± 0.26
7	3,5-$(CF_3)_2$	$C_{15}H_{13}N_3O_2F_6 \cdot C_2H_2O_4$	471.1	16	215	≥1600	>10
8	3,5-$(C(CH_3)_3)_2$	$C_{21}H_{31}N_3O_2 \cdot C_2H_2O_4 \cdot 0.25\,H_2O$	452.0	14	181	>1600	>10
9	2,4,6-$(CH_3)_3$	$C_{16}H_{21}N_3O_2 \cdot C_2H_2O_4 \cdot 0.5\,H_2O$	386.4	28	131	90 ± 14	>10
10	4-(CO-CH_3)	$C_{15}H_{17}N_3O_3 \cdot C_4H_4O_4 \cdot 0.25\,H_2O$	407.9	36	159	73 ± 15	>10
11	3-(CO-CH_3)	$C_{15}H_{17}N_3O_3 \cdot C_4H_4O_4 \cdot 0.25\,H_2O$	407.9	46	134	n.d.[b]	>10
Thioperamide[a]						4 ± 1	1.0 ± 0.5
Clobenpropit[a]						0.6 ± 0.1	26 ± 7

[a] ref. [20], [b] n.d. = not determined

H_1 and H_2 receptors, and at the muscarinic M_3 receptor (Table 2). On the peripheral histamine H_3 receptor all carbamates behaved as antagonists of moderate to high potency. The *in vitro* potencies of these substances in the central and peripheral functional H_3-receptor models (rat synaptosomes and guinea pig ileum) were compared by linear regression analysis. The correlation was not significant ($r = 0.332$, $p < 0.05$, regression analysis not shown). This may result from the rather small number of test compounds rather than from receptor or species inhomogeneity or detection of pre- or postsynaptic action [30].

The carbamates were tested for their H_1- and muscarinic M_3-receptor activity on guinea pig ileum and for their H_2-receptor activity on the guinea pig right atrium generally showing low activity for all compounds. The muscarinic M_3 receptor was selected because the functional H_3-receptor test on guinea pig ileum can be influenced by cholinergic innervation, predominantly an M_3-receptor-dependent effect.

As shown by data in Table 2, H_3-receptor antagonist activities of compounds **3–6** and **9–11** clearly predominate, thus these compounds are selective antagonists for the histamine H_3 receptor as well as for **3–6** being potent antagonists under *in vivo* conditions.

Table 2: Antagonist activities at histamine H_3-, H_2-, H_1-, and muscarine M_3-receptors for compounds 3–11

Compd.	H_3-receptor		H_2-receptor	H_1-receptor	M_3-receptor
	$-\log K_i$	$-\log K_B$	pD'_2	pD'_2 (pK_B)	pD'_2 (pK_B)
3	7.72	6.99	4.8	4.8	4.0
4	7.10	7.18	<4.5	<5.0	(4.8)
5	7.41	7.88	4.3	4.0	3.6
6	7.36	6.93	5.3	4.6	4.1
7	≤5.8	<6.0	3.7	<5.0	4.8
8	<5.8	<6.0	4.6	5.4	(5.4)
9	7.05	6.82	4.1	4.0	3.8
10	7.14	6.08	4.0	(4.1)	(4.6)
11	n.d.[a]	6.29	4.2	(4.6)	3.8

[a] n.d. = not determined

3. Experimental

3.1. Chemistry

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 WM AC 300 (300 MHz) spectrometer or on a Bruker DPX 400 Avance (400 MHz) spectrometer. Chemical shifts are expressed in ppm downfield from internal TMS as reference. ^{1}H NMR data are reported in the following order: multiplicity (br, broad; s, singlet; d, doublet; t, triplet; m, multiplet; asterisk, exchangeable by D_2O; Im, imidazole; Mal, maleic acid; Phe, phenylring); number of protons, and approximate coupling constants in Hertz (Hz). MS were obtained on Finnigan MAT CH 7A and Finnigan MAT CH5DF (Xenon, DMSO/Glycerin) (high-resolution mass spectra, HRMS). Spectral data of representative compounds for both synthetic ways are shown only (**5**, **10**, **7**, **8**). Elemental analyses (C, H, N) for all compounds were measured on Perkin-Elmer Elementaranalysator 240 B and 240 C or on Perkin-Elmer Elementar Vario EL instruments and were within ±0.4% of the theoretical values, unless otherwise stated. Preparative, centrifugally accelerated, rotatory chromatography was performed using a Chromatotron 7924T (Harrison Research) and glass rotors with 4 mm layers of silica gel 60 PF_{254} containing gypsum (Merck). TLC was performed on silica gel PF254 Plates (Merck), and the spots were visualized with fast blue salt BB.

3.1.1. General synthetic procedure for carbamates **1–6** *and* **9–11**

The carbamates were prepared from a solution of trichloromethyl chloroformiate (5.5 mmol) and a catalytic amount of activated charcoal in 20 ml of dry ethyl acetate to which the corresponding amine (5 mmol) solved in 10 ml of dry ethyl acetate was added dropwise. The reaction mixture was heated to reflux for 4–5 h, the black solution was cooled, filtered, and the solvent was evaporated carefully under reduced pressure. The freshly prepared isocyanate was dissolved in 20 ml of dry acetonitrile and added to 3-(1 *H*-imidazol-4-yl)-propanol · HCl (5 mmol) in 10 ml of dry acetonitrile [20]. The solution was refluxed again for 4–5 h, quenched by addition of 10 ml of methanol and concentrated in vacuo. The residue was purified by rotatory chromatography (eluent: $CHCl_3$/MeOH (gradient from 95 : 5 to 90 : 10), ammonia atmosphere). Separation was controlled by TLC (solvent $CHCl_3$/MeOH (9 : 1), ammonia atmosphere). The products were obtained as colourless oils and crystallized as hydrogen maleates (**1**, **2**, **4–6**, **10**, **11**) or as hydrogen oxalates (**3**, **9**) in Et_2O/EtOH.

3.1.1.1. *N*-(2-Ethylphenyl) 3-(1 *H*-imidazol-4-yl)propylcarbamate (**5**)

^{1}H NMR ([D_6]DMSO) δ = 8.88 (s, 1 H, Im-2-H), 8.81 (s, 1 H, NH*), 7.41 (s, 1 H, Im-5-H), 7.30–7.09 (m, 4H, Ph-H), 6.05 (s, 2 H, Mal), 4.07 (t, J = 6.4 Hz, 2 H, CH_2-O), 2.73 (t, J = 7.5 Hz, 2 H, Im-CH_2), 2.59 (m, 2 H, CH_2-CH_3), 1.97 (m, 2 H, CH_2-CH_2-O), 1.11 (t, J = 7.5 Hz, 3 H, CH_3); MS m/z 273 (23, $[M]^{+\cdot}$), 132 (14), 121 (30), 106 (100), 95 (44), 81 (33), 77 (23), 54 (12), 44 (24).

3.1.1.2. *N*-(4-Acetylphenyl) 3-(1 *H*-imidazol-4-yl)propylcarbamate (**10**)

^{1}H NMR ([D$_6$]DMSO); δ = 10.09 (s, 1 H, NH*), 8.89 (s, 1 H, Im-2-H), 7.91 (d, J = 8.4 Hz, 2 H, Ph-3-H, Ph-5-H), 7.59 (d, J = 8.4 Hz, 2 H, Ph-2-H, Ph-6-H), 7.44 (s, 1 H, Im-5-H), 4.16 (t, J = 6.3 Hz, 2 H, CH_2—O), 2.76 (t, J = 7.5 Hz, 2 H, Im-CH_2), 2.51 (s, 3 H, CH_3), 2.00 (m, 2 H, CH_2—CH_2—O); MS m/z 287 (20, $[M]^{+\cdot}$), 200 (16), 146 (15), 135 (64), 120 (100), 108 (27), 95 (58), 81 (40), 65 (25), 54 (12), 44 (83), 26 (10).

3.1.2. General synthetic procedure for carbamates **7** *and* **8**

The corresponding acid (5 mmol), triethylamine (5 mmol), and diphenyl phosphorazidate (DPPA) (5mmol) were dissolved in 30 ml of dry acetonitrile, stirred at ambient temperatures for 45 min and then heated to reflux for 30 min [31]. Subsequently 5 mmol of 3-(1 *H*-imidazol-4-yl)propanol · HCl were added, and the mixture was refluxed for ca. 40 h. The solvent was evaporated under reduced pressure, the residue dissolved in Et_2O, and extracted with a solution of citric acid (5%) and a saturated solution of $NaHCO_3$, 30 ml each. The solution was concentrated in vacuo, and the residue was purified by rotatory chromatography (eluent: $CHCl_3$/MeOH (gradient from 95 : 5 to 90 : 10), ammonia atmosphere). Separation was controlled by TLC (solvent: $CHCl_3$/MeOH (9 : 1), ammonia atmosphere). The products were obtained as colourless oils and crystallized as hydrogen oxalates in Et_2O/EtOH.

3.1.2.1. *N*-[3,5-Bis(trifluoromethyl)phenyl] 3-(1 *H*-imidazol-4-yl)propyl-carbamate (**7**)

^{1}H NMR ([D$_6$]DMSO); δ = 10.44 (s*, 1 H, CO-NH), 8.80 (s, 1 H, Im-2-H), 8.12 (s, 2 H, Ph-2-H, Ph-6-H), 7.67 (s, 1 H, Ph-4-H), 7.37 (s, 1 H, Im-5-H), 4.15 (m, 2 H, CH_2—O), 2.74 (m, 2 H, Im-CH_2), 2.00 (m, 2 H, CH_2—CH_2—O); MS m/z 382 (41, $[M+H]^+$), 109 (100), 95 (24), 81 (57), 41 (15); CHN; N calcd 8.28, found, 7.12; HRMS; calcd 381.091, found 381.091.

3.1.2.2. *N*-[3,5-Di(*tert*-butyl)phenyl]3-(1 *H*-imidazol-4-yl)propylcarbamate (**8**)

^{1}H NMR ([D$_6$]DMSO) δ = 9.47 (s*, 1 H, CO-NH), 8.58 (s, 1 H, Im-2-H), 7.35 (s, 2 H, Ph-2-H, Ph-6-H), 7.27 (s, 1 H, Ph-4-H), 7.04 (s, 1 H, Im-5-H), 4.09 (t, J = 6.1 Hz, 2 H, CH_2—O), 2.73 (t, J = 7.2 Hz, 2 H, Im-CH_2), 1.97 (m, 2 H, CH_2-CH_2-O), 1.25 (s, 18 H, 6 CH_3); MS m/z 357 (28, $[M]^{+\cdot}$), 231 (45), 216 (100), 126 (27), 109 (74), 95 (37), 82 (32), 57 (31), 45 (32).

3.2. Pharmacology, general methods

3.2.1. Histamine H_3-receptor in vitro assay on synaptosomes of rat cerebral cortex

Histamine H_3-receptor antagonist activities of compounds **1**–**10** were tested in an assay using K^+-evoked depolarization-induced release of [^{3}H]histamine from synaptosomes of rat cerebral cortex according to the procedure described by Garbarg et al. [21]. The data presented are given as mean values with standard error for a minimum of three separate determinations each.

3.2.2. Histamine H_3-receptor antagonist in vivo assay in mice

The increase in levels of the main histamine metabolite, N^τ-methylhistamine, in Swiss mice brain 90 min after p.o. administration of the test compounds **1**–**11** (Table 1) was evaluated to determine histamine H_3-receptor antagonist potency *in vivo* [21]. ED_{50} values were calculated as mg of free base · kg^{-1} and shown as a mean with standard error.

3.2.3. Histamine H_3-receptor antagonist in vitro assay on guinea pig ileum

Histamine H_3-receptor activity was also 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 antagonists **3**–**11** [22]. All values represent the mean of at least five separate determinations.

3.2.4. Histamine H_1-, H_2-, and muscarinic M_3-receptor in vitro 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 activities and on the spontaneously beating right atrium for H_2-receptor activity according to Hirschfeld et al. and Ligneau et al. [23, 24].

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