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Acylated and alkylated histamine derivatives as new histamine H_3-receptor antagonists

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Summary — New histamine H_3-receptor antagonists were prepared and investigated for their ability to increase synthesis and release of histamine mediated by inhibition of presynaptically located H_3-receptors. Acyl derivatives of histamine methylated at different positions show poor activity at H_3-receptors, whereas N^{α}-alkyl and particularly N^{α}-acyl derivatives of histamine possess moderate to good H_3-receptor antagonist activity. A not-too-bulky and lipophilic residue in an optimal distance of 3–4 methylene groups from the amide function leads to potent and selective H_3-receptor antagonists. N^{α}-Histamine-γ-phenylbutyramide **11** and N^{α}-histamine-γ-cyclohexylbutyramide **13** are H_3-receptor antagonists with – log K_i of 7.1 and 7.3, respectively. Structure–activity relationships of different substitution patterns are discussed.

histamine / histamine H_3-receptor antagonist / N^{α}-alkylated histamine / N^{α}-acylated histamine / N^{α}-histamine-γ-cyclohexylbutyramide

Introduction

The existence of a third histamine receptor subtype was suggested in 1983 with the discovery that synthesis and release of histamine in slices of rat cerebral cortex are modulated by a receptor subtype pharmacologically distinct from histamine H_1- and H_2-receptors [1]. This presynaptically located autoreceptor was named the histamine H_3-receptor. Nowadays, it can be shown that H_3-receptors also function as heteroreceptors on serotoninergic [2], cholinergic [3], noradrenergic [4], dopaminergic [5] and peptidergic [6] neurons. It was proposed that H_3-receptor antagonists influence cerebral functions like microcirculation and vigilance [7] by modulating the release of histamine as well as other neurotransmitters.

In the agonist field only minor modifications of the endogenous ligand are accepted by the H_3-receptor without loss of activity (for review, see [8]). Potent and selective compounds are (*R*)-(–)-α-methylhistamine [9], (*Rα,Sβ*)-*α,β*-dimethylhistamine [10] and imetit [11]. In the antagonist field the discovery of thioperamide, a potent and selective H_3-receptor antagonist [9], related acyl derivatives [12], and recently developed isothioureas, *eg*, VUF 9153 (fig 1 [13]), made it possible to evaluate cerebral H_3-receptors *in vitro* and in animals *in vivo*. The clinical safety of these drugs was never demonstrated, but it seems useful to develop histamine H_3-receptor antagonists of a new chemical series for potential clinical evaluation.

Our starting point was the observation that the simplest acyl derivative of the endogenous ligand, N^{α}-acetylhistamine **1**, shows moderate H_3-receptor antagonist activity (fig 1). By variation of acyl or alkyl substituents of the primary amino group of histamine or different methylated histamine derivatives the antagonist activity should be increased without increasing the toxicity.

The N^{α}-acylated and N^{α}-alkylated histamines and comparable compounds were investigated for their H_3-receptor antagonist *in vitro* activity using slices of rat-brain cortex [9]. For selected compounds the activity at other histamine receptor subtypes was determined to check their selectivity towards histamine H_3-receptors.

Chemistry

The compounds were prepared according to scheme 1. The methylated histamine derivatives that were used

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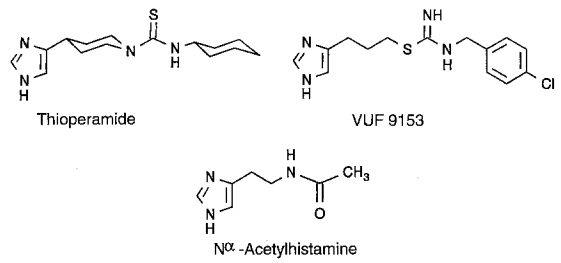
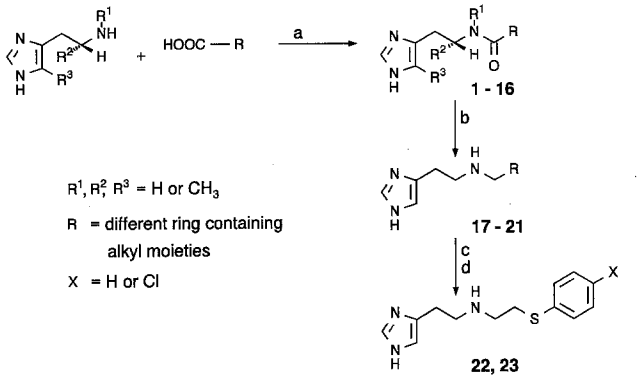


Fig 1. Structures of histamine H_3-receptor antagonists.



Scheme 1. Reagents: a) 1,1'-carbonyldiimidazole in tetrahydrofuran; b) $POCl_3/NaBH_4$ in diglyme; c) 47% HBr; d) sodium arylthiolate in ethanol.

as starting materials for compounds **12**, **14** and **15** were obtained according to known methods [14, 15]. Acylation of the amines was performed under mild conditions by reaction with the corresponding carboxylic acid after activation with 1,1'-carbonyldiimidazole. The amides could be separated from the imidazole equivalents and purified by rotationary chromatography. Activation of the amide group with phosphorus oxychloride and following hydrogenation with sodium borohydride afforded the secondary amines with fewer by-products than reduction by other methods. Preparation of the arylthioethers **22**, **23** was performed *via* ether cleavage of **21** in 47% HBr and following alkylation of the corresponding arylthioles in alkaline medium.

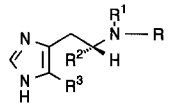
Pharmacology

The new compounds were tested for their H_3-receptor antagonist activity in an assay with K^+-evoked depolarisation-induced release of [^{3}H]histamine from slices of rat-brain cortex [9]. The K_i-values were determined according to the Cheng–Prusoff equation [16]. The data presented are given as mean values with standard error of the mean for a minimum of 3 separate determinations each. Selected compounds were screened for histamine H_2-receptor agonist activity at isolated spontaneously beating guinea-pig right atrium as well as for H_1-receptor agonist/ antagonist activity at isolated guinea-pig ileum by standard methods [14, 17].

Results and discussion

The presented N^{α}-histamine derivatives all possess moderate to pronounced H_3-receptor antagonist activity (tables I and II).

Table I. Histamine H_3-receptor antagonist activity of N^{α}-acylated histamine derivatives.



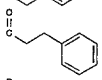
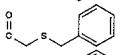
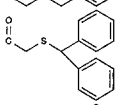
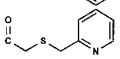
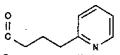
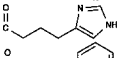
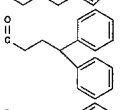
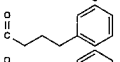
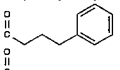
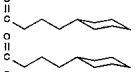
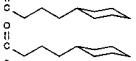
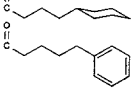
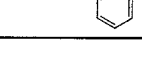
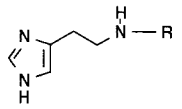
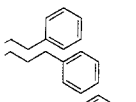
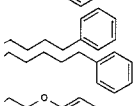
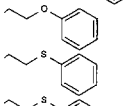
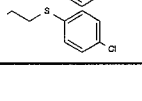
Compound	R^1	R^2	R^3	R	K_i ($\bar{x}\pm s_{\bar{x}}$) [M]	-log K_i
1	H	H	H		$1.4\pm0.1 \times 10^{-6}$	5.9
2	H	H	H		$1.0\pm0.2 \times 10^{-6}$	6.0
3	H	H	H		$6.3\pm1.0 \times 10^{-7}$	6.2
4	H	H	H		$8.0\pm2.3 \times 10^{-7}$	6.1
5	H	H	H		$6.8\pm2.4 \times 10^{-7}$	6.2
6	H	H	H		$1.1\pm0.1 \times 10^{-6}$	6.0
7	H	H	H		$1.8\pm0.8 \times 10^{-6}$	5.7
8	H	H	H		$9.2\pm4.9 \times 10^{-7}$	6.0
9	H	H	H		$1.1\pm0.3 \times 10^{-6}$	6.0
10	H	H	H		$1.1\pm0.6 \times 10^{-6}$	6.0
11	H	H	H		$7.6\pm2.2 \times 10^{-8}$	7.1
12	H	CH_3	H		$1.1\pm0.4 \times 10^{-6}$	6.0
13	H	H	H		$5.4\pm1.8 \times 10^{-8}$	7.3
14	CH_3	H	H		$1.3\pm0.5 \times 10^{-5}$	4.9
15	H	H	CH_3		$>1.0 \times 10^{-5}$	<5.0
16	H	H	H		$2.1\pm1.0 \times 10^{-7}$	6.7

Table II. Histamine H_3-receptor antagonist activity of N^{α}-alkylated histamine derivatives.



Compound	R	K_i ($\bar{x}\pm s_{\bar{x}}$) [M]	-log K_i
17		$3.5\pm2.6 \times 10^{-6}$	5.5
18		$6.7\pm2.4 \times 10^{-7}$	6.2
19		$7.0\pm3.4 \times 10^{-7}$	6.2
20		$2.2\pm0.5 \times 10^{-6}$	5.7
21		$4.1\pm1.7 \times 10^{-7}$	6.4
22		$2.5\pm1.2 \times 10^{-6}$	5.6
23		$2.5\pm2.1 \times 10^{-7}$	6.6

While there is no difference in activity between the acetyl derivative **1** and the phenylacetyl derivative **2**, the homologous phenylpropionyl derivative **3** shows slightly higher activity at histamine H_3-receptors. Exchange of 1 methylene group by oxygen or sulphur has no advantage on H_3-receptor activity (**4–7**, **21**, **22**). The optimal distance between the polar amide function and the hydrophobic ring substituent seems to be of special importance (**2**, **3**, **11**, **16**). One phenyl ring at a distance of 3 methylene groups **11** is the optimum in the series of ω-arylalkylamides. Bulkier residues like the diphenyl group (**6**, **10**) or more hydrophilic moieties like the pyridine (**7**, **8**) or imidazole (**9**) rings fail to increase H_3-receptor affinity. N^{α}-Histamine-γ-phenylbutyramide **11** shows a $-\log K_i$ of 7.1 at the histamine H_3-receptor. Replacement of the phenyl ring by a saturated cyclohexyl ring as in thioperamide leads to the compound with the highest biological activity in the amide series (**13**; $-\log K_i$ = 7.3). Introduction of a methyl group in the 5-position of the imidazole ring (**15**) or in the α-position of the histamine side chain (**12**) as well as methylation of the N^{α}-atom (**14**) in each case led to a evident decrease in H_3-receptor blocking activity. Although (*R*)-(–)-α-methylhistamine and N^{α}-methylhistamine are both potent H_3-receptor agonists, the corresponding amides **12** and **14** are moderate or weakly active H_3-receptor antagonists. This observation indicates distinct binding sites for H_3-receptor agonists and antagonists.

Changing the amide group to a secondary amine leads to compounds bearing totally different basicity as well as different steric and electronic parameters. Although the amines are dissimilar in their physicochemical properties to the corresponding amides they possess remarkable H_3-receptor antagonist activity (table II), but this new class of compounds failed to improve the H_3-receptor blocking activity. The amines show similar structure–activity relationships as those described above for amides. A chain length of 3–4 methylene groups between the amine group and the phenyl ring seems to be the optimal spacer. Compared to the unsubstituted aromatic ring a *para*-chloro substitution (**23**) leads to a significant increase of the H_3-receptor antagonist activity. Similar structure–activity relationships were reported for H_3-receptor antagonists of the isothiourea series [13].

Lipophilic aromatic and alicyclic rings like the phenyl or the cyclohexyl ring are preferred for high histamine H_3-receptor affinity. Bulkier or hydrophilic residues lead to a loss in H_3-receptor activity. This suggests that the interaction between antagonist and H_3-receptor depends on a hydrophobic pocket rather than on electrostatic π-π interactions at this binding site.

The H_3-receptor antagonists of the amine type **17–23** show only very weak or no H_1- and H_2-receptor agonist activity but moderate H_1-receptor antagonist activity (table III). It seems that the introduction of an ether linkage (**21**) decreases the H_1-receptor blocking activity while a thioether linkage (**22**) retains it (*cf* **18**); the H_3-receptor selectivity of these compounds is less pronounced. Introduction of a lipophilicity enhancing chloro-substituent (**23**) increases the H_1- and

Table III. Selectivity of selected compounds at histamine receptor subtypes.

Compound	H_3 $-\log K_i$	H_2 ia^a	H_1 ia^a	H_1 $-\log K_i$
11	7.1	0	0	4.2
17	5.5	0	0.11	
18	6.2	0.25	0	5.1
19	6.2	0.18	0.34	
20	5.7	0.11	0.38	
21	6.4	0	0	3.9
22	5.6	0	0	5.0
23	6.6	0	0.1	5.5

[a]ia = intrinsic activity (related to histamine, ia = 1).

Table IV. Analytical data of compounds **2–23**.

Compound	*Formula*[a] *(Molecular weight)*	*Melting point (°C) (Solvent)*	*Yield (%)*	*Mass spectra m/z*[b]	*^{1}H-NMR(δ in ppm) TMS as internal standard*
2	$C_{13}H_{15}N_3O$ (229.3)	161–164 (EtOH/Et_2O)	84	229	8.12 (br*, 1H, NH-CO), 7.53 (s, 1H, Im-2-H), 7.33-7.19 (m, 5H, Phe), 6.76 s, 1H, Im-5-H), 3.40 (s, 2H, CH_2-Phe), 3.28 (dt, $J_1 = J_2 = 6.8$ Hz, 2H, CHN), 2.63 (t, $J = 7.4$ Hz, 2H, CH_2-Im)
3	$C_{14}H_{17}N_3O$ (243.3)	131–135 (EtOH/Et_2O)	81	243	7.88 (br, 1H, NH-CO), 7.49 (d, $J = 1.5$ Hz, 1H, Im-2-H), 7.26-7.09 (m, 5H, Phe), 6.74 (d, $J = 1.5$ Hz, 1H, Im-5-H), 3.27 (dt, $J_1 = J_2 = 6.9$ Hz, 2H, CH_2-N), 2.83-2.35 (m, 6H, CH_2-Im, CH_2-CH_2-Phe)
4	$C_{13}H_{15}N_3O_2$ (245.3)	87–88 (EtOH/Et_2O)	83	245	8.22 (br, 1H, NH-CO), 7.54 (s, 1H, Im-2-H), 7.33 (m, 2H, Phe-3,5-H), 6.97 (m, 3H, Phe-2,4,6-H), 6.80 (s, 1H, Im-5-H), 4.46 (s, 2H, CH_2-O), 3.37 (dt, $J_1 = J_2 = 7$ Hz, CH_2-N), 2.68 (t, $J = 7$ Hz, 2H, CH_2-Im)
5	$C_{14}H_{17}N_3OS$ (275.4)	136–138 (EtOH/Et_2O)	67	275	8.09 (br*, 1H, NH-CO), 7.55 (d, $J = 0.8$ Hz, 1H, Im-2-H), 7.36-7.21 (m, 5H, Phe), 6.82 (d, $J = 0.8$ Hz, 1H, Im-5-H), 3.77 (s, 2H, CH_2-Phe), 3.31 (dt, $J_1 = J_2 = 7$ Hz, 2H, CH_2-N), 3.03 (s, 2H, CH_2-CO), 2.66 (t, $J = 7$ Hz, 2H, Im-CH_2)
6	$C_{20}H_{21}N_3OS$ (351.5)	165 (EtOH/Et_2O)	85	352	8.05 (br*, 1H, NH-CO), 7.55 (d, $J = 0.8$ Hz, 1H, Im-2-H), 7.43-7.21 (m, 10H, 2Phe), 6.82 (d, $J = 0.8$ Hz, 1H, Im-5-H), 5.36 (s, 1H, CH-S), 3.28 (dt, $J_1 = J_2 = 7$ Hz, 2H, CH_2-N), 2.98 (s, 2H, CH_2-S), 2.63 (t, $J = 7$ Hz, Im-CH_2)
7	$C_{13}H_{16}N_4OS$ (276.4)	96 (EtOH/Et_2O)	68	276	8.52 (d, $J = 2.8$ Hz, 1H, Pyr-6-H), 8.46-7.15 (m, 4H, Pyr-3,4,5-H, Im-2-H), 6.77 (s, 1H, Im-5-H), 3.85 (s, 2H, CH_2-Pyr), 3.45-3.21 (m, 2H, CH_2-N), 3.11 (s, 2H, CH_2-CO), 2.62 (t, $J = 6.8$ Hz, 2H, Im-CH_2)
8	$C_{14}H_{18}N_4O$ (258.3)	131–134 (EtOH/Et_2O)	18	258	12.10 (br*, 1H, Im-NH), 8.47 (m, 1H, Pyr-6-H), 7.88 (br*, 1H, NH-CO), 7.69 (dt, $J_1 = 1.9$ Hz, $J_2 = 7.4$ Hz, 1H, Pyr-4-H), 7.52 (s, 1H, Im-2-H), 7.24-7.17 (m, 2H, Pyr-3,5-H), 6.78 (s, 1H, Im-5-H), 3.26 (dt, $J_1 = J_2 = 6.8$ Hz, 2H, CH_2-N), 2.73-2.59 (m, 4H, Im-CH_2, Pyr-CH_2), 2.09 (t, $J = 7.3$ Hz, 2H, CH_2-CO),1.88 (quin, $J = 7.5$ Hz, 2H, CH_2-CH_2-CH_2)
9	$C_{12}H_{17}N_5O$ •2Mal (479.5)	106–108 (EtOH/MeCN)	42	247	8.79-8.71 (m, 2H, 2 Im-2-H), 8.08 (br*, 1H, NH-CO), 7.30 (m, 2H, 2 Im-5-H), 6.11 (s, 4H, 2CH=CH), 3.33 (dt, $J_1 = J_2 = 6.5$ Hz, 2H, CH_2-N), 2.88-2.51 (m, 6H, 2CH_2-Im, CH_2-CO), 2.04 (m, 2H, CH_2-CH_2-CH_2)
10	$C_{21}H_{23}N_3O$ (333.4)	183 (EtOH/Et_2O)	24	333	7.80 (br*, 1H, NH-CO), 7.45 (s, 1H, Im-2-H), 7.32-7.23 (m, 10H, 2Phe), 6.71 (s, 1H, Im-5-H), 3.99 (t, $J = 7.3$ Hz, 1H, CH), 3.33 (dt, $J_1 = J_2 = 6$ Hz, 2H, CH_2-N), 2.64 (t, $J = 6$ Hz, 2H, Im-CH_2), 2.48-2.04 (m, 4H, CH_2-CH_2-CO)
11	$C_{15}H_{19}N_3O$ (257.3)	167 (EtOH/Et_2O)	43	257	11.81 (br*, 1H, Im-NH), 7.88 (br*, 1H, NH-CO), 7.52 (s, 1H, Im-2-H), 7.31-7.14 (m, 5H, Phe), 6.78 (s, 1H, Im-5-H), 3.27 (dt, $J_1 = J_2 = 6.8$ Hz, 2H, CH_2-N), 2.65-2.52 (m, 4H, Phe-CH_2, Im-CH_2), 2.07 (t, $J = 7.5$ Hz, 2H, CH_2-CO), 1.78 (quin, $J = 7.5$ Hz, 2H, CH_2-CH_2-CH_2)
12	$C_{16}H_{21}N_3O$ (271.4)	106–108 (EtOH/Et_2O)	59	271	11.83 (br*, 1H, Im-NH), 7.72 (br*, 1H, NH-CO), 7.52 (s, 1H, Im-2-H), 7.28-7.04 (m, 5H, Phe), 676 (s, 1H, Im-5-H), 4.05-3.97 (m, 1H, CH), 2.71-2.56 (m, 4H, CH_2-Im, CH_2-Phe), 2.06 (t, $J = 7.1$ Hz, 2H, CH_2-CO), 1.83-1.74 (m, 2H, CH_2-CH_2-CH_2), 1.01 (d, $J = 6.4$ Hz, 3H, CH_3)
13	$C_{15}H_{25}N_3O$ (263.4)	109–110 (THF)	53	263	11.80 (br*, 1H, Im-NH), 7.86 (br*, 1H, NH-CO), 7.51 (d, $J = 0.7$ Hz, 1H, Im-2-H), 6 83 (d, $J = 0.7$ Hz, 1H, Im-5-H), 3.24 (dt, $J_1 = J_2 = 6.8$ Hz, 2H, CH_2-N), 2.55 (t, $J = 6.8$ Hz, 2H, Im-CH_2), 2.01 (t, $J = 7.4$ Hz, 2H, CH_2-CO), 1.67-0.79 (m, 15H, 7CH_2, 1CH)
14	$C_{16}H_{27}N_5O$ •Mal•0.5H_2O (402.5)	93 (EtOH/Et_2O)	34	277	8.88 (s, 1H, Im-2-H), 7.41 (s, 1H, Im-5-H), 6.06 (s, 2H, Mal), 3.54 (m, 2H, CH_2-NH), 2.93-2.79 (m, 5H, Im-CH_2, NH-CH_3), 2.20 + 2.10 (2t, $J = 7.3$ Hz, 2H, CO-CH_2), 1.67-0.81 (m, 15H, 7CH_2, CH)
15	$C_{16}H_{27}N_3O$ •Mal•0.5H_2O (402,5)	125.5 (EtOH/Et_2O)	60	275	8.83 (s, 1H, Im-2-H), 7.85 (t*, 1H, NH-CO), 6.03 (s, 2H, Mal), 3.26 (m, 2H, CH_2-NH), 2 68 (t, $J = 6.5$ Hz, 2H, Im-CH_2), 2.18 (s, 3H, Im-CH_3), 1.98 (t, $J = 7.4$ Hz, 2H, CO-CH_2), 1.71 (m, 2H, CH_2-CH_2-NH), 1.66-0.79 (m, 15H, 7CH_2, CH)
16	$C_{16}H_{21}N_3O$ (271.4)	134 (EtOH/Et_2O)	59	271	11.80 (br*, 1H, Im-NH), 7.86 (br*, 1H, NH-CO), 7.51 (s, 1H, Im-2-H), 7.31-7.13 (m, 5H, Phe), 6.76 (s, 1H, Im-5-H), 3.25 (dt, $J_1 = J_2 = 7$ Hz, 2H, CH_2-N), 2.65-2.57 (m, 4H, Im-CH_2, Phe-CH_2), 2.07 (t, $J = 6.5$ Hz, 2H, CH_2-CO), 1.51 (m, 4H, CH_2-CH_2-CH_2-Phe)
17	$C_{13}H_{17}N_3$•2HCl (288.2)	235–238 (EtOH/MeCN)	45	289	9.59 (br*, 2H, NH_2^+), 9.08 (d, $J = 1$ Hz, 1H, Im-2-H), 7.57 (d, $J = 1$ Hz, 1H, Im-5-H), 7.38-7.23 (m, 5H, Phe), 3.32-3.40 (m, 4H, CH_2-NH_2^+-CH_2), 3.16 (t, $J = 6.8$ Hz, 2H, Im-CH_2), 3.01 (m, 2H, CH_2-Phe)
18	$C_{14}H_{19}N_3$•2HCl (302.2)	208–210 [20] (EtOH/MeCN)	26	229	9.73 (br*, 2H, NH_2^+), 9.03 (d, $J = 1.4$ Hz, Im-2-H), 7.51 (d, $J = 1.4$ Hz, 1H, Im-5-H), 7.39-7.26 (m, 5H, Phe), 3.20 (br, 4H, CH_2-NH_2^+-CH_2), 2.98-2.50 (m, 4H, CH_2-Im, CH_2-Phe), 2.03 (m, 2H, CH_2-CH_2-CH_2)
19	$C_{15}H_{21}N_3$•2HCl (316,3)	221–222 (EtOH/MeCN)	26	243	14.76 (br*, 2H, 2 Im-NH), 9.39 (br*, 2H, NH_2^+), 9.08 (s, 1H, Im-2-H), 7.55 (s, 1H, Im-5-H), 7.32-7.15 (m, 5H, Phe), 3.24 (br, 2H, CH_2-CH_2-Im), 3.15 (t, $J = 6.5$ Hz, 2H, CH_2-CH_2-CH_2-N), 2.93 (br, 2H, CH_2-Im), 2.50 (t, $J = 6.7$ Hz, 2H, CH_2-Phe), 1.66 (m, 4H, CH_2-CH_2-CH_2-Phe)
20	$C_{16}H_{23}N_3$•2HCl (330.5)	204–205 (EtOH/MeCN)	41	257	14.73 (br*, 2H, 2 Im-NH), 9.40 (br*, 2H, NH_2^+), 9.08 (s, 1H, Im-2-H), 7.56 (s, 1H, Im-5-H), 7.32-7.15 (m, 5H, Phe), 3.26-3.22 (m, 2H, CH_2-CH_2-Im), 3.15 (t, $J = 6.5$ Hz, 2H, CH_2-CH_2-CH_2-N), 2.89-2.84 (m, 2H, CH_2-Im), 2.61 (t, $J = 7.6$ Hz, 2H, CH_2-Phe), 1.76-1.53 (m, 4H, CH_2-CH_2-CH_2-CH_2-Phe), 1.36-1.23 (m, 2H, CH_2-CH_2-CH_2-Phe)
21	$C_{13}H_{17}N_3O$•2HCl (304,2)	205–207 (EtOH/Et_2O)	50	232	14.74 (br*, 2H, 2 Im-NH), 9.68 (br*, 2H, NH_2^+), 9.09 (d, $J = 1$ Hz, 1H, Im-2-H), 7.56 (d, $J = 1$ Hz, 1H, Im-5-H), 7.34 (m, 2H, Phe-3,5-H), 6.99 (m, 3H, Phe-2,4,6-H), 4.32 (t, $J = 5$ Hz, 2H, CH_2-O), 3.37 (m, 4H, CH_2-NH_2^+-CH_2), 3.19 (t, $J = 7.3$ Hz, 2H, CH_2-Im)
22	$C_{13}H_{17}N_3S$•2HCl (320.3)	167 (EtOH/Et_2O)	57	248	d = 9.00 (s, 1H, Im-2-H), 7.51 (s, 1H, Im-5-H), 7.45-7.22 (m, 5H, Phe), 3.51-3.28 (m, 6H, CH_2-NH_2^+-CH_2, CH_2-Im), 3.13-3.07 (m, 2H, CH_2-S)
23	$C_{13}H_{16}ClN_3S$•2HCl (354.7)	206–207 (EtOH/MeCN)	45	282	14.58 (br*, 2H, 2 Im-NH), 9.80 (br*, 2H, NH_2^+), 9.07 (d, $J = 1.2$ Hz, 1H, Im-2-H), 7.54-7.40 (m, 5H, Phe, Im-5-H), 3.41-3.27 (m, 4H, CH_2-NH_2^+-CH_2), 3.17-3.07 (m, 4H, CH_2-Im, CH_2-S)

[a]All compounds were microanalysed. Anal (C, H, N); [b]all spectra EI-MS except for compounds **17**, **21**, **22** and **23** where $^+$FAB-MS spectra were recorded; compound **1** is commercially available. Abbreviations; Mal = maleic acid ($C_4H_4O_4$), Phe = phenyl, Im = imidazole, Pyr = pyridine, *exchangeable with D_2O.

H_3-receptor antagonist potency by 3- and 10-fold, respectively **22**, **23**. In contrast to the amines, the investigated amide **11** shows no agonistic activity at H_1- and H_2-receptors and only very low antagonistic activity at histamine H_1-receptors. The activity of the prepared antagonist **11** is about 3 orders of magnitude higher at H_3-receptors than at H_1- or H_2-receptors. Thus the histamine H_3-receptor antagonists described in this paper are both effective and selective.

Conclusion

The presented histamine derivatives of the amide and amine type are moderate to good H_3-receptor antagonists [18]. Acyl derivatives of histamines methylated in different positions are compounds with poor H_3-receptor activity. In general the amides are more potent than the corresponding amines. Lipophilic and not too bulky substituents like a phenyl or cyclohexyl group at a distance of 3–4 methylene groups from the amide function lead to potent H_3-receptor antagonists. Compounds **11** and **13** are the most effective H_3-receptor antagonists of this series. N^{α}-Histamine-γ-phenylbutyramide **11** also shows high selectivity towards the H_3-receptor subtype. Therefore histamine H_3-receptor antagonists of this type can be used for further investigations concerning the physiological and pharmacological functions mediated by histamine H_3-receptors.

Experimental protocols

Chemistry

Melting points are uncorrected and were determined by using a Büchi 512 Dr Tottoli apparatus. ^{1}H-NMR spectra were recorded on a Bruker WC 300 spectrometer with tetramethylsilane (TMS) as an internal standard. Samples of free bases were dissolved in $CDCl_3$ and the salts in DMSO-d_6. Elemental analyses were performed on Perkin–Elmer 240B and Perkin–Elmer 240C instruments. Analyses indicated by the symbols of elements or functional groups were within ± 0.4% of the theoretical values. Mass spectra were recorded using Finnigan MAT CH7A (70 eV), Finnigan MAT 711 (80 eV), Kratos MS 25 RF (70 eV) or, in case of $^+$FAB spectra, a Finnigan MAT CH5DF instrument (xenon, DMSO/glycerol). Chromatographic separation was done by rotationary chromatography using a chromatotron Model 7924T (Harrison Research) with 4 mm layers of silica gel 60 PF_{254} containing gypsum (Merck) with $CHCl_3$/methanol (gradient from 99:1 to 90:10) in an ammonia atmosphere. All analytical data are presented in table IV. The nomenclature in this article is based on histamine substitution according to Black and Ganellin [19].

*General procedure for amide synthesis **1–16***
1,1'-Carbonyldiimidazole (10 mmol) was dissolved in 15 ml tetrahydrofuran with an equimolar amount of the carboxylic acid. After 30 min, 10 mmol of the amine was added and the mixture was stirred for 14 h. The solvent was removed under reduced pressure and purified *via* chromatography. Some amides were transformed into hydrogen maleates by the standard method.

*General procedure for amine synthesis **17–21***
The amide (5 mmol) was stirred for 14 h in 30 ml phosphorus oxychloride at ambient temperature. After evaporation under reduced pressure to eliminate the solvent, the remaining oil was redissolved in 40 ml diglyme with 25 mmol $NaBH_4$ at 5°C. The solution was hydrolyzed after 5 h with 17.5 ml 10% HCl for 14 h. Subsequent evaporation to dryness, dissolution in 30 ml water, washing with CH_2Cl_2, basification with 3 g NaOH and extraction with CH_2Cl_2 gave an organic phase which could be dried by addition of Na_2SO_4 and evaporated to result in an oil which mainly consisted of the amine. Chromatographic purification and transformation into a salt was performed to obtain the corresponding amine in an analytically pure, easy to handle form.

*Arylthioethers **22–23***
Compound **21** (14 mmol) was heated under reflux with 30 ml 47% HBr for 4 d under a nitrogen atmosphere. The resulting solution was evaporated to dryness and N^{α}-(2-bromoethyl)-histamine•2HBr [20] crystallized with diethylether/2-propanol to yield 56% slightly brown crystals which were pure enough for further reaction. The bromo compound was added to solutions of 8 mmol sodium in 25 ml absolute ethanol containing 2.5 mmol thiophenol or 4-chlorothiophenol. After heating under reflux for 3 h, evaporation to dryness, and dissolution in water at pH 12 the compounds were extracted with CH_2Cl_2, dried over Na_2SO_4 and purified *via* chromatography.

Pharmacology

The compounds were tested according to the methods mentioned in the pharmacological section. They were dissolved in DMSO and diluted in water, or dissolved in water when they were applied in form of their salts.

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