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Synthesis and histamine H_3-receptor agonist activity of mono- and dialkyl-substituted histamine derivatives†

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Summary — In search for potential histamine H_3-receptor agonists a series of mono- and dialkyl-substituted histamine derivatives was synthesized. All target compounds were tested *in vitro* for their agonist activity at H_3-, H_2-, and H_1-receptors. Introduction of one ethyl or two methyl residues into histamine led to compounds with decreased histamine H_3-agonist potency in most cases. However, the non-chiral α,α-dimethylhistamine (**15**) was identified to be three times as active as histamine itself at H_3-receptors. In addition **15** shows high receptor selectivity being 20 000 times as active at H_3- as at H_2- and H_1-receptors, respectively. (α*R*)-α,N^{τ}-Dimethylhistamine **23**, which is a potential metabolite of (α*R*)-α-methylhistamine **1**, proved to be inactive at all three histamine receptor subtypes.

α,α-dimethylhistamine / (αR)-α,N^{τ}-dimethylhistamine / histamine H_3-receptor / agonist

Introduction

Since the discovery of the third histamine receptor in 1983 [1], several studies have clearly demonstrated that this receptor is distinct from the previously known H_2- and H_1-receptor subtypes [2–5].

The histamine H_3-receptor is located presynaptically on histaminergic neurons where it modulates the synthesis and release of histamine. The activation of the H_3-receptor by an agonist leads to a decrease in the concentration of the neurotransmitter histamine in the synaptical cleft [6]. More recently, H_3-heteroreceptors have also been found on cholinergic [7], dopaminergic [8], noradrenergic [9], serotonergic [10] and peptidergic [11] neurons.

Early investigations demonstrated the existence of histamine H_3-receptors in the central nervous systems (CNS) as well as in the peripheral tissues of several species [12–14], and its existence in the human brain has since been demonstrated [15]. From a series of alkyl-substituted histamine derivatives, (α*R*)-α-methylhistamine [16] (**1**, EC_{50} = 4.0 nM, rat brain, see fig 1) was selected to be the first H_3-receptor agonist for clinical trials with human volunteers [17]. Within these studies, its potential therapeutic value with respect to diseases in the CNS and in the respiratory and the gastrointestinal fields was investigated.

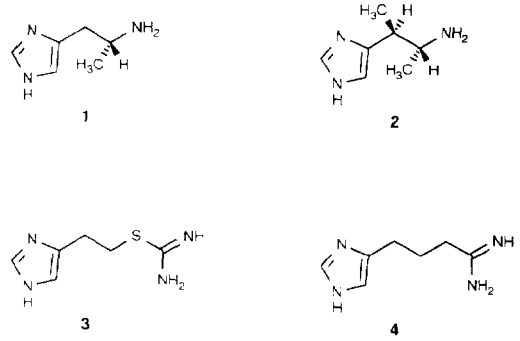

Fig 1. Structures of compounds **1–4**.

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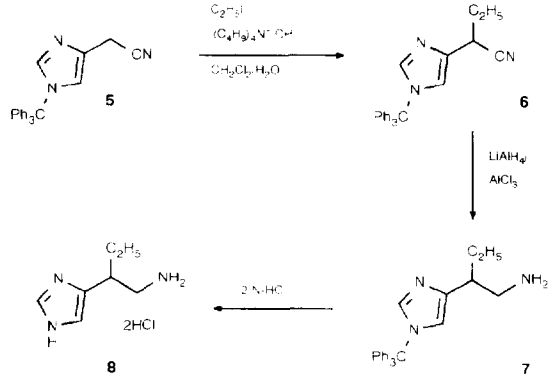
Further attempts to design and synthesize new H_3-receptor agonists led to highly potent and selective compounds, both in a series of histamine derivatives ((*R*α,*S*β)-α,β-dimethylhistamine, **2**, EC_{50} = 3.4 nM, rat brain) [18] and in a series of imidazolylalkane derivatives bearing an isothiourea moiety (Imetit, **3**, K_i = 4.6 nM, guinea-pig ileum) or positively charged groups like an amidine group (SK&F 91606, **4**, K_i = 1.1 nM, guinea-pig ileum) [19–22]. Very recently, an additional highly active histamine H_3-receptor agonist has been identified: Immepip [23, 24].

The objective of this study was to identify further potent and selective histamine H_3-receptor agonists. Additional alkyl-substituted histamine derivatives have been synthesized and screened for their *in vitro* activity at the three histamine receptor subtypes.

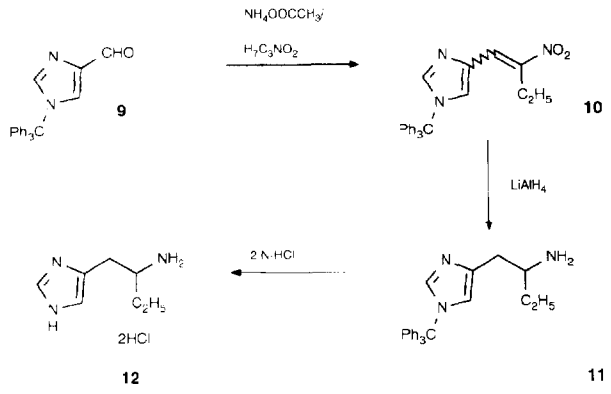
Chemistry

Ethylation of **5** was carried out according to Brändström and Junggren [25] in a binary solvent system of CH_2Cl_2 and water with ethyl iodide (see scheme 1). Applying the 20-fold excess of alkylating agent resulted in a mixture consisting of about 70% **6** and 15% of the related dialkylated product; 15% of the starting material remained unchanged (all values according to visual check of thin-layer chromatograms). After chromatographical purification, **6** was reduced to the corresponding amine in the presence of $LiAlH_4/AlCl_3$. Subsequent acid detritylation led to the deblocked amine **8**.

Knoevenagel reaction of **9** in the presence of acetic ammonia and *n*-nitropropane led to compound **10** (see scheme 2). Unfortunately, it was not possible to determine the *E*/*Z*-ratio of the geometrical isomers of the latter by ^{1}H-NMR spectroscopy due to overlapping with signals of the trityl residue. A simultaneous reduction of the nitro group and double bond of **10**



Scheme 1.



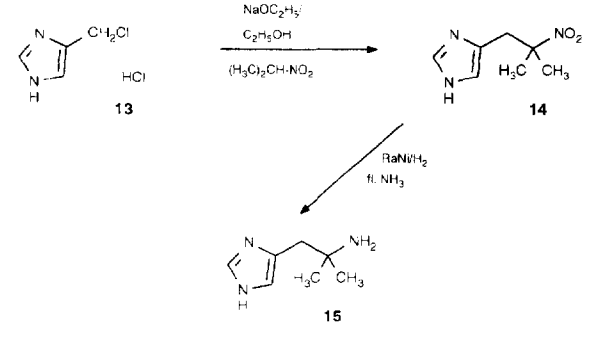
Scheme 2.

was carried out using $LiAlH_4$. The obtained **11** was subsequently deblocked in the presence of HCl, which led to the corresponding amine **12**.

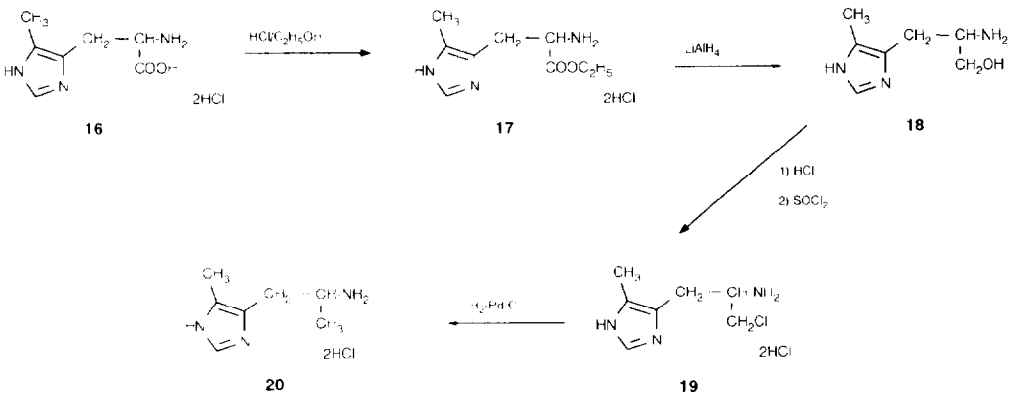
Nucleophilic substitution of the chloro atom of **13** by means of deprotonated 2-nitropropane mainly led to the alkylation product **14** (see scheme 3). Hydrogenation of the latter over basic Raney nickel was carried out in liquid ammonia at 40°C and 27 MPa, resulting in the amine **15**.

Esterification of 5-methylhistidine **16** in EtOH/HCl led to **17** and was followed by $LiAlH_4$ reduction (see scheme 4). The obtained alcohol **18** was converted into the corresponding chloromethyl derivative **19**. Reductive dehalogenation of the latter was carried out using hydrogen over Pd/C and led to the desired amine **20**.

Compound **21** is a versatile (α*R*)-α-methylhistamine derivative which is simultaneously blocked at the side-chain nitrogen and at the N^{π} of the imidazole nucleus (see scheme 5). Therefore, it could be methylated selectively at the unblocked N^{τ} using methyl



Scheme 3.



Scheme 4.

iodide. The obtained **22** was hydrolyzed in 57% HI which led to the disubstituted histamine derivative **23** in one step.

Pharmacology

All the mono- and dialkylated histamine derivatives examined in this investigation turned out to be full agonists at histamine H_3-receptors. However, there were striking differences in their relative potencies (table I).

Results and discussion

One of these compounds, α,α-dimethylhistamine **15**, proved to be even more potent than histamine itself, displaying three times the activity of the latter. The other dimethyl-substituted histamine derivatves **20**, **23** and β,β-dimethylhistamine are rather weak H_3-receptor agonists showing relative potencies of 0.04, 0.14, and 3.6%, respectively (relative potency of histamine 100%). In addition the α- and β-mono- substituted compounds **8** and **12** are also weak agonists at H_3-receptors.

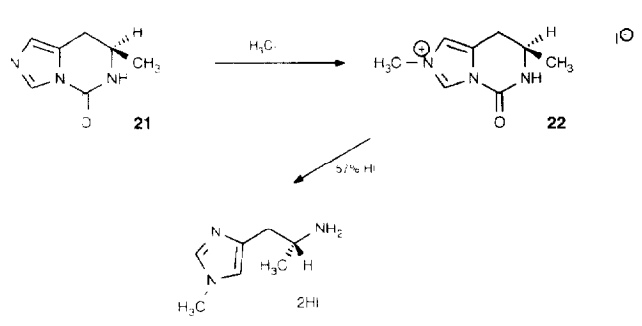
Comparison of these data with earlier results obtained for (α*R*)-α-methylhistamine (relative potency = 1550% [16]) and β-methylhistamine (relative potency = 282% [26]) clearly shows that the introduction of a second methyl group in either the α-, 5- or N^{τ}-position diminishes the activity in comparison with the parent molecule. This diminishing effect is less pronounced in the case of **15**, where both methyl groups are allocated in the α-position of the side chain. This is of special interest, since the second methyl group was introduced in an *S*-configuration in **1**. Therefore, **15** formally represents an overlay of highly potent **1** and its distomer (α*S*)-α-methylhistamine, which is a weak H_3-receptor agonist displaying a relative potency of only 13% [16].

Although most of the compounds investigated in this study do not show reasonable H_3-receptor selectivity, α,α-dimethylhistamine **15** is about 20 000 times more potent at H_3-receptors than at both H_2- and H_1-receptors.

Despite its low H_3-agonist activity, compound **23** is rather interesting, since it represents a potential metabolite of the potent H_3-agonist, (α*R*)-α-methylhistamine **1**, which is widely used as a reference in both *in vitro* and *in vivo* trials. Therefore, **23** will be a useful tool to investigate whether **1** is subjected to the most important step of histamine metabolism in brain, N^{τ}-methylation [27].

Conclusion

The newly characterized mono- and dialkyl-substituted histamine derivatives represent an interesting group of compounds. They may serve as pharmacological tools and be valuable for quantitative structure–activity relationship calculations to further characterize the



Scheme 5.

Table I. Comparison of H_3-, H_2-, and H_1-receptor agonist activities (EC_{50} [M]) of histamine and its mono- and disubstituted derivatives.

Compound	*H_3-Agonism, inhibition of [^{3}H]histamine release*		*H_2-Agonism, atrial rate*		*H_1-Agonism, ileum contraction*	
	EC_{50}	*ia*	*EC_{50}*	*ia*	*EC_{50}*	*ia*
Histamine	$6.2 \pm 1.4 \times 10^{-8}$	1	$1.0 \pm 0.3 \times 10^{-6}$	1	$1.4 \pm 0.9 \times 10^{-7}$	1
(±)-β-Ethylhistamine **8**	$1.0 \pm 0.5 \times 10^{-5}$	1	$6.1 \pm 1.4 \times 10^{-4}$	0.59	$1.0 \pm 0.1 \times 10^{-4}$	0.79
(±)-α-Ethylhistamine **12**	$1.1 \pm 0.6 \times 10^{-5}$	1	8.5×10^{-5}	0.84	1.3×10^{-4}	1
α,α-Dimethylhistamine **15**	$2.3 \pm 1.1 \times 10^{-8}$	1	$5.2 \pm 4.1 \times 10^{-4}$	0.43	$3.6 \pm 2.0 \times 10^{-4}$	0.66
(±)-α,4(5)-Dimethylhistamine **20**	$1.4 \pm 0.3 \times 10^{-4}$	1	1.5×10^{-5} [33]	0.82 [33]	6.1×10^{-5} [33]	0.77 [33]
(−)-(α*R*)-α,N^{τ}-Dimethylhistamine **23**	3.0×10^{-5}	1	nc[a]	0.33	1.3×10^{-4}	0.77
(±)-β,β-Dimethylhistamine[b]	$1.7 \pm 0.8 \times 10^{-6}$	1	na[c]	na[c]	1.1×10^{-4} [42]	0.79 [42]

In general EC_{50} values are given as mean ± sem and were calculated from data of 3–4 independent *in vitro* experiments (except H_3 data of **23**, H_2 data of **12**, and H_1 data of **12** and **23**). Calculation of EC_{50} values at H_3-receptors was carried out according to Parker and Waud [39] whereas statistical evaluation of the data for H_1- and H_2-agonism was performed according to Sachs [40]. Intrinsic activity (ia) is given relative to histamine. [a]Not calculated due to ia of below 0.4. [b]Synthesized according to [41]. [c]Not available.

relationship calculations to further characterize the H_3-receptor subtype. The non-chiral α,α-dimethylhistamine **23** is a potent and selective H_3-receptor agonist.

Experimental protocols

Chemistry

General procedures

Melting points were not corrected and were determined using a Büchi 512 Dr Tottoli apparatus. Elemental analyses were performed on Perkin Elmer 240B and Perkin Elmer 240C instruments at the analytical department of the Institut für Pharmazie, Freie Universität, Berlin. Analyses indicated by the symbols of the elements were within ±0.4% of theoretical values. ^{1}H-NMR spectra were recorded on Bruker WP 60, Bruker WM 250 or Bruker WC 300 spectrometers with TMS as an internal standard. EI-MS 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-MS spectra, a Finnigan MAT CH5DF instrument (xenon, DMSO/glycerol). A Perkin-Elmer 241 MC polarimeter was used. Column chromatography was carried out using silica gel 63-200 µm (Machery & Nagel). A Chromatotron 7924T (Harrison Research) equipped with glass plates, covered with 4 mm layers of silica gel 60 PF_{254} containing gypsum (Merck), was also used for preparative purification. The nomenclature of substituted histamine derivatives is based on Black and Ganellin [35].

2-[1-(Triphenylmethyl)-1H-imidazol-4-yl]butanenitrile **6**

A solution of 42.44 g (125 mmol) tetrabutyl ammonium hydrogensulphate and 10 g (250 mmol) NaOH in 125 ml water was added to a solution of compound **4** (8.74 g, 25 mmol, 2-[1-(triphenylmethyl)-1*H*-imidazol-4-yl]ethane nitrile, prepared according to DeGraw *et al* [28]) and 77.99 g (0.5 mol) ethyl iodide in 50 ml CH_2Cl_2. The resulting mixture was stirred vigorously and refluxed for 3 h. The organic layer was then removed, dried over Na_2SO_4 and evaporated. Extraction of the resulting oil by means of Et_2O and evaporation was followed by chromatographical purification (Chromatotron; petroleum ether/Et_2O, (3:1)). Crystallization from Et_2O afforded 3.91 g (41.4%) **6** in the form of white crystals, mp = 128–130°C. EI-MS: *m/z* (rel int, %) = 377 ($M^{+\bullet}$, < 1), 262 (5), 243 (100), 165 (29). ^{1}H NMR (60 MHz, DMSO-d_6): δ = 7.54–7.03 (m, 16H, Im-2-H, 3•phe), 6.86 (d, *J* = 1 Hz, 1H, Im-5-H), 3.77 (d, *J* = 6.4 Hz, 1H, CH), 2.27–2.03 (qd, J_1 = 7.4 Hz, J_2 = 6.4 Hz, 2H, CH_2), 1.06 (t, *J* = 7.4 Hz, 3H, CH_3). Anal $C_{26}H_{23}N_3$ (C, H, N).

2-[1-(Triphenylmethyl)-1H-imidazol-4-yl]butanamine **7**

A solution of 0.53 g $AlCl_3$ in 15 ml THF was added to a suspension of 0.15 g (4 mmol) $LiAlH_4$ in 15 ml THF. A solution of 1.32 g (3.5 mmol) **6** in 15 ml THF was then added dropwise and after stirring for 1 h the mixture was hydrolyzed by addition of 0.8 ml water and 1.6 ml 5 N NaOH. The precipitate was removed and washed with CH_2Cl_2. The combined organic layers were dried over $CaCl_2$, evaporated and the resulting oil chromatographically purified (Chromatotron; $CHCl_3$/MeOH (99:1) ammoniacal atmosphere). For analytical purposes a small amount of the resulting oily 0.90 g (67.6%) **7** was converted into the dihydrochloride and recrystallized from EtOH, resulting in **7**•2HCl•H_2O, mp = 171°C. EI-MS: *m/z* (rel int, %) = 380 ($M^{+\bullet}$, < 1), 352 (3), 243 (100), 165 (59), 95 (7), 81 (2). ^{1}H NMR (250 MHz, DMSO-d_6): δ = 8.12 (br, exchangeable by D_2O, 3H, NH_3^+), 7.56 (s, 1H, Im-2-H), 7.46–7.08 (m, 15H, 3•phe), 6.83 (s, 1H, Im-5-H), 3.99 (br, 2H, CH_2-N), 2.83–2.79 (m, 1H, CH), 1.66–1.51 (m, 2H, CH_2-CH_3), 0.69 (t, *J* = 7.3 Hz, 3H, CH_3). Anal $C_{26}H_{27}N_3$•2HCl•H_2O (C, H, N).

2-(1H-Imidazol-4-yl)butanamine dihydrochloride **8**

A solution of 0.45 g (1.2 mmol) **7** in 20 ml of 2 N HCl was refluxed for 2 h. After cooling to ambient temperature and filtration the solution was washed with 20 ml Et_2O in two portions. Evaporation, crystallization by adding petroleum ether and recrystallization from MeOH/MeCN yielded 0.22 g (82.9%) **8**•0.5H_2O in the form of white crystals, mp = 181–183°C. EI-MS: *m/z* (rel int, %) = 139 ($M^{+\bullet}$, 2),126 (48), 95 (100), 81 (8). ^{1}H NMR (250 MHz, DMSO-d_6): δ = 9.12 (d, *J* =

1.3 Hz, 1H, Im-2-H), 8.25 (br, exchangeable by D_2O, 3H, NH_3^+), 7.53 (d, J = 1.3 Hz, 1H, Im-5-H), 3.14 (br, 3H, $CHCH_2N$), 2.57–2.49 (m, 2H, CH_2CH_3), 0.76 (t, J = 7.3 Hz, 3H, CH_2). Anal $C_7H_{13}N_3$•2HCl•0.5H_2O (C, H, N).

4-(2-Nitro-1-butenyl)-1-(triphenylmethyl)-1H-imidazole ***10***
A mixture of 5.00 g (14.8 mmol) of compound **9** [1-(triphenylmethyl)-1*H*-imidazol-4-yl]methanal, prepared according to Bernabé and Burger [29]) and 0.40 g (5.2 mmol) NH_4OAc in 50 ml nitropropane was stirred at 100°C for 5 h. Upon cooling to ambient temperature compound **10** precipitated and was recrystallized from CCl_4, mp = 215–216°C. Yield 3.80 g (62.7%). EI-MS: *m/z* (rel int, %) = 409 (M^+•, < 1), 243 (100), 166 (10), 165 (73). ^{1}H NMR (60 MHz, $CDCl_3$): δ = 7.77 (s, 1H, C*H*-Im), 7.56 (d, J = 1.3 Hz, 1H, Im-2-H), 7.47–7.04 (m, 17H, 3•phe, Im-5-H, CH=CNO_2), 3.27 (q, J = 7.2 Hz, 2H, CH_2), 1.18 (t, J = 7.2 Hz, 3H, CH_3). Anal $C_{26}H_{23}N_3O_2$ (C, H, N).

1-[1-(Triphenylmethyl)-1H-imidazol-4-yl]-2-butanamine ***11***
Compound **10** (1.00 g, 2.4 mmol) was added to a suspension of 0.38 g (10 mmol) $LiAlH_4$ in 20 ml THF. After stirring for 3 h at ambient temperature the reaction mixture was hydrolyzed by addition of 20 ml water. THF was evaporated *in vacuo* and **11** was dissolved in the form of its hydrochloride by addition of 1 N HCl. Filtration, extraction by means of 2-butanol and evaporation were followed by dissolution in 1 N HCl. The resulting solution was washed with CH_2Cl_2 and made alkaline by addition of 1 N NH_3. Extraction with CH_2Cl_2, drying over Na_2SO_4, evaporation, addition of MeCN and bubbling HCl through the solution resulted in 0.26 g (23.1%) **11**•2HCl•0.75H_2O, mp = 162–163°C. $^+$FAB-MS: *m/z* (rel int, %) = 382 ([M+H]$^+$, 39), 243 (100), 165 (25). ^{1}H NMR (250 MHz, DMSO-d^6): δ = 8.96 (s, 1H, Im-2-H), 8.45 (br, exchangeable by D_2O, 3H, NH_3^+), 7.53–7.26 (m, 16H, 3•phe, Im-5-H), 3.51–3.49 (m, 1H, C*H*-NH_3^+), 2.98 (d, J = 6.7 Hz, 2H, CH_2-Im), 1.69–1.52 (m, 2H, CH_2CH$_3$), 0.91 (t, J = 7.4 Hz, 3H, CH_3). Anal $C_{26}H_{27}N_3$•2HCl•0.75H_2O (C, H, N).

1-(1H-Imidazol-4-yl)-2-butanamine dihydrochloride ***12***
A solution of 0.33 g (0.7 mmol) **11**•2HCl•0.5H_2O in 20 ml 1 N HCl was stirred at 60°C for 0.5 h. After cooling to ambient temperature, filtration and evaporation, excess HCl was removed and the residue obtained was dissolved in EtOH. Addition of Et_2O led to 0.12 g (83.0%) **12** in the form of white crystals, mp = 210°C. $^+$FAB-MS: *m/z* (rel int, %) = 140 ([M+H]$^+$, 89), 123 (12), 93 (100), 82 (8) 74 (36). ^{1}H NMR (250 MHz, DMSO-d_6): δ = 9.08 (d, J = 1.1 Hz, 1H, Im-2-H), 8.27 (br, exchangeable by D_2O, 3H, NH_3^+), 7.55 (d, J = 1.1 Hz, 1H, Im-5-H), 3.39 (m, 1H, C*H*NH_3^+), 3.01 (d, J = 6.8 Hz, 2H, CH_2-Im), 1.59 (dq, $J_1 = J_2$ = 7.3 Hz, 2H, CH_2CH$_3$) , 0.94 (t, J = 7.3 Hz, 3H, CH_3) . Anal $C_7H_{13}N_3$•2HCl (C, H, N).

4-(2-Methyl-2-nitropropyl)-1H-imidazole ***14***
2-Nitropropane (7.34 g, 82.5 mmol) was added to a solution of 3.80 g (165.2 mmol) Na in 200 ml dry MeOH. After stirring for 0.5 h at ambient temperature the mixture was cooled to 0°C and 12.66 g (84.4 mmol) **13** (4-chloromethyl-1*H*-imidazole hydrochloride, prepared according to Pyman [30]) were added. Stirring for 2 h at ambient temperature, filtration from precipitated NaCl, column chromatography ($CHCl_3$/MeOH (9:1) saturated with ammonia) and crystallization by adding EtOAc resulted in 8.50 g (59.5%) **14**, mp = 108–109°C. EI-MS: *m/z* (rel int, %) = 169 (M^+•, 21), 123 (78), 122 (61), 95 (14), 82 (14), 81 (100), 55 (18). ^{1}H NMR (60 MHz , $CDCl_3$): δ = 7.56 (d, J = 1.3 Hz, 1H, Im-2-H), 6.83 (d, J = 1.3 Hz, 1H, Im-5-H), 3.23 (s, 2H, CH_2), 1.62 (s, 6H, 2CH_3). Anal $C_7H_{11}N_3O_2$ (C, H, N).

1-(1H-Imidazol-4-yl)-2-methyl-2-propanamine ***15***
Compound **14** (3.90 g, 23.0 mmol) was dissolved in 250 ml liquid ammonia and hydrogenated for 3 d at 40°C and 27 bar over freshly prepared basic Raney nickel [31]. After evaporation and addition of 200 ml water, the catalyst was removed by filtration. Dissolved Ni-ions were precipitated by bubbling H_2S through the solution. Excess H_2S was removed by heating. Subsequently 6 N HCl was added until pH 1 was reached and the mixture was evaporated to dryness. Addition of dry EtOH, filtration and evaporation yielded 2.81 g (57.6%) **15** which was subsequently recrystallized from MeOH/MeCN, mp = 234°C. MS: *m/z* (rel int, %) = 139 (M^+•, 2), 124 (4), 82 (51), 58 (100), 36 (44). ^{1}H-NMR: (60 MHz, DMSO-d_6): δ = 8.88 (d, J = 1 Hz, ^{1}H, Im-2-H), 7.49 (d, J = 1 Hz, 1H, Im-5-H), 3.04 (s, 2H, CH_2), 1.29 (s, 6H, 2CH_3). Anal $C_7H_{13}N_3$•2HCl (C, H, N).

Ethyl 2-amino-3-(5-methyl-1H-imidazol-4-yl)propanoate dihydrochloride ***17***
HCl was bubbled through a solution of 7.00 g (28.9 mmol) 2-amino-3-(5-methyl-1*H*-imidazol-4-yl)propanoic acid dihydrochloride (compound **16**, prepared according to Trout [32]) in EtOH and the mixture was refluxed for 4 h. Upon cooling and evaporation 7.12 g (91.2%) compound **17** crystallized. After washing with acetone a small sample was recrystallized several times from EtOH for analytical purposes, mp = 250–254°C. EI-MS: *m/z* (rel int, %) = 197 (M^+•,17), 124 (23), 69 (100), 81 (10), 74 (48), 58 (32). ^{1}H NMR (60 MHz, DMSO-d_6): δ = 9.01 (s, 1H, Im-2-H), 4.37–3.99 (m, 3H, CH_2O, CH), 3.28 (d, J = 7.3 Hz, 2H, CH_2-Im), 2.26 (s, 3H, Im-CH_3), 1.16 (t, J = 7.1 Hz, 3H, CH_2CH_3). Anal $C_9H_{15}N_3O_2$•2HCl (C, H, N).

2-Amino-3-(5-methyl-1H-imidazol-4-yl)propanol ***18***
A suspension of 2.85 g (75 mmol) $LiAlH_4$ in 125 ml THF was cooled with ice. Subsequently 6.73 g (25.0 mmol) of **17** were added and the mixture was refluxed for 3 h. After cooling to 0°C the mixture was hydrolyzed by addition of a solution of 6 ml water in 60 ml THF. Upon evaporation *in vacuo*, **18** was extracted by means of EtOH from the residual material. Bubbling dry HCl gas through the resulting solution led to 3.51 g (52.0%) of **18** in the form of its dihydrochloride. A small amount of this material was converted into the dipicrate for analytical purposes, mp = 182–183°C (EtOH). EI-MS (obtained from **18**•2HCl): *m/z* (rel int, %) = 141 (M^+•, 6), 127 (8), 85 (30), 71 (29), 57 (28), 45 (100). ^{1}H NMR (obtained from **18**•2HCl; 250 MHz, DMSO-d_6): δ = 8.96 (s, 1H, Im-2-H), 8.29 (br, exchangeable by D_2O, 3H, NH_3^+), 5.51 (br, exchangeable by D_2O, 1H, OH), 3.58–3.45 (m, 3H, $CHCH_2O$), 2.96 (d, J = 4.3 Hz, 2H, CH_2-Im), 2.26 (s, 3H, CH_3). Anal $C_7H_{13}N_3O$•2$C_6H_3N_3O_7$ (C, H, N).

1-Chloro-3-(5-methyl-1H-imidazol-4-yl)-2-propanamine dihydrochloride ***19***
A solution of 1.90 g (8.4 mmol) **18**•2HCl and 15 ml $SOCl_2$ in 20 ml tetramethylene sulfone was stirred for 12 h at ambient temperature. Upon dropwise addition of 150 ml $CHCl_3$ 1.32 g (61.5%) **19** precipitated in form of a hygroscopic solid. A small sample was converted into the dipicrate and recrystallized from EtOH for the purpose of elemental analysis, mp = 149–152°C. EI-MS: (obtained from **19**•2HCl) *m/z* (rel int, %) 175/173 (M^+•, < 1/< 1), 137 (7), 120 (4), 109 (9), 96 (20), 95 (32), 56 (15), 41 (100). ^{1}H NMR (60 MHz, DMSO-d_6): δ = 8.83 (s, 1H, Im-2-H), 6.50 (br, exchangeable by D_2O, 3H, NH_3^+), 3.94–3.68 (m, 3H, CH_2Cl, C*H*NH_3^+), 3.18–2.91 (m, 2H, CH_2), 2.26 (s, 3H, Im-CH_3). Anal $C_7H_{12}ClN_3$•2$C_6H_3N_3O7$•0.5H_2O (C, H, N).

1-(5-Methyl-1H-imidazol-4-yl)-2-propanamine dihydrochloride ***20***
Compound **19** (1.00 g, 4.1 mmol) and 0.65 g (8.1 mmol) NaOAc were dissolved in 100 ml of 10% AcOH. After addition of 0.5 g Pd/C (10%) the resulting mixture was hydrogenated for 10 d at ambient temperature. After filtration from the catalyst, the obtained filtrate was adjusted to pH 1 by addition of 10 N HCl. Upon evaporation to dryness and dissolution in water-free EtOH, inorganic material crystallized and was removed. Addition of petroleum ether led to a solid material which was recrystallized from MeOH/MeCN and resulted in 0.32 g (36.8%) **20**, mp = 223–224°C (223–224°C [33]). EI-MS: *m/z* (rel int, %) 139 (M^{+}•, 3), 96 (100), 81 (6), 44 (49), 36 (52). ^{1}H NMR (60 MHz, DMSO-d_6): δ = 14.63 (br, exchangeable by D_2O, 2H, 2-Im-NH), 9.09 (s, 1H, Im-2-H), 8.93 (br, exchangeable by D_2O, 3H, NH_3^+), 3.84–3.15 (m, 1H, CH-N), 3.07 (br, CH_2-Im), 2.30 (s, 3H, Im-CH_3), 1.25 (d, J = 7.4 Hz, 3H, CHCH_3). Anal $C_7H_{13}N_3$•2HCl (C, H, N).

(R)-(–)-2,7-Dimethyl-5-oxo-5,6,7,8,-tetrahydroimidazo[1,5-c]-pyrimidin-2-ium iodide ***22***
Compound **21** (0.33 g, 2.2 mmol, prepared according to Gerhard and Schunack [34]), was dissolved in 20 ml DMF and 6.00 g (4.2 mmol) methyl iodide were added. After stirring at ambient temperature for 14 h and subsequent evaporation of the mixture the solid residual was recrystallized from 2-PrOH/MeOH yielding 0.52 g (80.6%) of **22**, mp: 214°C. EI-MS: *m/z* (rel int, %) 165 ([M-H]$^+$•), 151 (22), 128 (21), 127 (8), 96 (17), 95 (100), 42 (31). ^{1}H NMR (300 MHz, DMSO-d_6): δ =9.68 (s, 1H, C-3-H), 9.05 (s, exchangeable by D_2O, 1H, NH), 7.60 (s, 1H, C-1-H), 3.89–3.80 (m, 4H, N-CH_3, CH_M), 3.16 (dd, $^2J_{AM}$ = 16 Hz, $^3J_{AM}$ = 4.4 Hz, 1H, H_A of CH_2), 2.74 (dd, $^2J_{AB}$ = 16 Hz, $^3J_{BM}$ = 9.6 Hz, 1H, H_B of CH_2), 1.24 (d, J = 6.5 Hz, 3H, C-CH_3). $[\alpha]_D^{20}$ = –26.2(0.7)° (MeOH, c = 0.5). Anal $[C_8H_{12}N_3O]^+$• I– (C, H, N).

(R)-(–)-1-(1-Methyl-1H-imidazol-4-yl)-2-propanamine dihydroiodide ***23***
A solution of 0.40 g (1.4 mmol) of **22** in 20 ml 57% HI was kept under reflux for 3 d. After evaporation *in vacuo*, the remaining solid material was recrystallized from EtOH, yielding 0.23 g (41.6%) of **23** in form of colorless crystals, mp: 179–181°C. $^+$FAB-MS: *m/z* (rel int, %) 140 ([M+H]$^+$, 100), 123 (20). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.06 (s, 1H, Im-2-H), 7.85 (br, exchangeable by D_2O, 3H, NH_3^+), 7.57 (s, 1H, Im-5-H), 3.85 (s, 3H, N-CH_3), 3.58–3.50 (m, 1H, $CHNH_3^+$), 2.96 (dd, J_1 = 15 Hz, J_2 = 6.1 Hz, 1H, CH_2), 2.85 (dd, J_1 = 15 Hz, J_2 = 7.8 Hz, 1H, CH_2) 1.19 (d, J = 6.4 Hz, 3H, CCH_3). $[\alpha]_D^{20}$ = –1.2(0.3)° (MeOH, c = 0.5). Anal $C_7H_{13}N_3$•2HI (C, H, N).

Pharmacological evaluation

H_3-Receptor agonist activity on slices of rat brain cortex
Male Wistar rats (170–190 g) were killed by decapitation and brains were immediately removed. Slices of 0.3 mm thickness from cerebral cortex were preincubated for 30 min with [^{3}H]L-histidine (0.3 μM). After extensive washing, aliquots of the slice suspension (2–3 mg protein) were incubated at 37°C for 2 min in the presence of 2 or 30 mM KCl (final concentration). The slices were preincubated for 5 min before the depolarizing stimulus in the presence of the various drugs tested as agonists. Incubations were stopped by rapid centrifugation, and [^{3}H]histamine levels present in tissue and medium were quantified as described previously [1].

H_2-Receptor agonist activity on the isolated spontaneously beating guinea-pig right atrium
Male guinea pigs (350–500 g) were sacrificed by a blow to the head. The heart was removed and incubated in McEvans' solution [36] at 32.5°C, which was gassed with carbogen. The right atrium was separated, placed in a 20 ml organ bath containing McEvans' solution. After a equilibration time of 1 h, isometric impulses were recorded by a heart frequency meter. Each preparation was used only for one single test. To test the H_2-receptor agonist activity histamine standard curves (10^{-7}–10^{-5} M concentration in the bath) were recorded using a cumulative technique. After washing from histamine the potential H_2-receptor agonist was tested by recording a concentration–response curve [37].

H_1-Receptor agonist activity on the isolated guinea-pig ileum
Male guinea pigs (350–500 g) were sacrificed by a blow to the head. Pieces of the ileum 3 cm in length were incubated in a 20 ml organ bath containing Tyrode solution at 37°C, which was aerated with carbogen. Contraction effects were isotonically recorded. In order to determine the agonist activity of a compound a histamine standard curve was first recorded. Therefore histamine concentration was geometrically increased in the bath until maximal contraction of the ileum was reached [38]. After thorough washing a concentration–response curve of the potential agonist was recorded in the same way.

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