The Effect of Lipophilic Substituents on the H_2-Histaminergic Activity of Some Close Analogues of Impromidine[+)**)]

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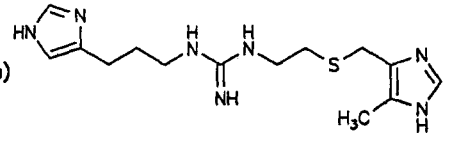
The cimetidine-like moiety of the potent H_2-agonist impromidine (**9a**) and three closely related guanidines (**10a**, **11a**, and **12a**) which are modified in the imidazolylpropyl portion, has been replaced by 2-[(2-pyridyl)methylthio]ethyl, 2-(benzylthio)ethyl and 3,3-diphenylpropyl substituents. Guanidines **10-12** were obtained from acidic hydrolysis of corresponding *N*-benzoyl guanidines **7**, **8**, and **15**, accessible by successive aminolysis of diphenyl *N*-benzoyl carbonimidate (**2**) according to known methods. Compared with leads **10a** and **11a** lipophilic substitution affords almost equipotent H_2-agonists **10b-d** and **11b-d**, while substituents with increasing lipophilicity enhance both intrinsic activity and potency of the weak partial agonist **12a** at guinea-pig atrial H_2-receptors. Guanidines **10-12** are weak H_1-antagonists on the isolated guinea-pig ileum.

Der Einfluß lipophiler Substituenten auf die H_2-histaminerge Aktivität einiger Impromidin-Analoga

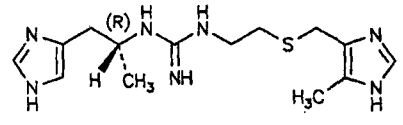
Der cimetidinähnliche Substituent des potenten H_2-Agonisten Impromidin (**9a**) sowie dreier nahe verwandter Guanidine (**10a**, **11a** und **12a**), die eine Modifikation in der Imidazolylpropyl-Gruppierung aufweisen, wurde durch 2-[(2-Pyridyl)methylthio]ethyl-, 2-(Benzylthio)ethyl- und 3,3-Diphenylpropyl-Reste ersetzt. Die Guanidine **10-12** wurden durch saure Hydrolyse aus den entspr. *N*-Benzoylguanidinen **7**, **8** und **15** erhalten; letztere waren nach bekannter Methodik durch schrittweise Aminolyse von Diphenyl-*N*-benzoylimidocarbonat (**2**) zugänglich. Verglichen mit den Leitstrukturen **10a** und **11a** ergibt eine lipophile Substitution jeweils nahezu äquipotente H_2-Agonisten **10b-d** und **11b-d**, wohingegen zunehmend lipophile Reste sowohl die intrinsische Aktivität als auch die Potenz des schwachen partiellen Agonisten **12a** am H_2-Rezeptor des Meerschweinchen-Atriums deutlich verstärken. Die Guanidine **10-12** sind schwache H_1-Antagonisten am isolierten Meerschweinchen-Ileum.

Since the introduction of impromidine (**9a**) as a highly potent selective H_2-agonist[1] numerous publications dealing with structure-activity relationships of impromidine-type H_2-agonists have appeared. The results have clearly demonstrated the major importance of the guanidine[2,3] and 3-(1*H*-imidazol-4-yl)propyl moiety[2-5] for an effective full agonism at atrial H_2-receptors. Only a few attempts to replace the efficacy-causing imidazolylpropyl substituent have been successful so far, leading to the chiral guanidine sopromidine[6] and a series of 3-(2-aminothiazol-5-yl)propyl analogues[7] of both **9a** and arpromidine (Scheme 1). On the other hand the cimetidine-like partial structure in **9a** can be replaced by either alternative moieties known from H_2-antagonists[4,8-10] or by H_2-nonspecific lipophilic groups[10-21]. Among these compounds arpromidine (Scheme 1) and halogenated analogues[11,12] justify special mention as promising positive inotropic agents more potent than impromidine *in vivo* and *in vitro*. Additionally a more beneficial profile of action with respect to lower stimulating effects on heart rate and reduced arrhythmogenic potential *in vivo* has been reported[22-24].

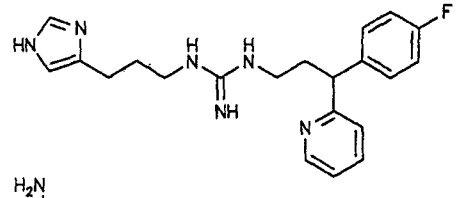
impromidine (**9a**)



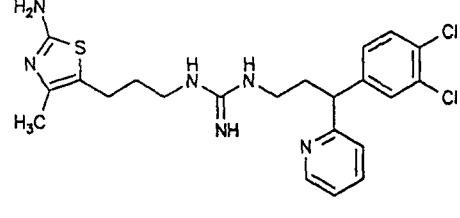
sopromidine



arpromidine



2-aminothiazole analogue



Scheme 1

In the present study the effect of a lipophilic H_2-nonspecific substitution on the H_2-agonistic activity of three closer analogues of the classical H_2-agonist fragment [3-(1*H*-imidazol-4-yl)propyl]guanidine was investigated. The leads selected for lipophilic modification, *i.e.* **10a**, **11a**, and **12a** (Scheme 2), have recently been reported to possess moderate (**10a**, **11a**) or very weak (**12a**) H_2-agonistic activity as compared with impromidine[4].

Chemistry

The guanidines **10b-d**, **11b-d**, and **12b-d** were prepared according to a known method[14] using diphenyl *N*-benzoyl carbonimidate (**2**)[25] as a source of the central guanidine unit (Scheme 2). Thus the amines **1b-d** were first treated with **2** in CH_2Cl_2, followed by aminolysis of the resulting

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**) Dedicated to Prof. Dr. Dr. *E. Mutschler*, Frankfurt am Main, on the occasion of his 60th birthday

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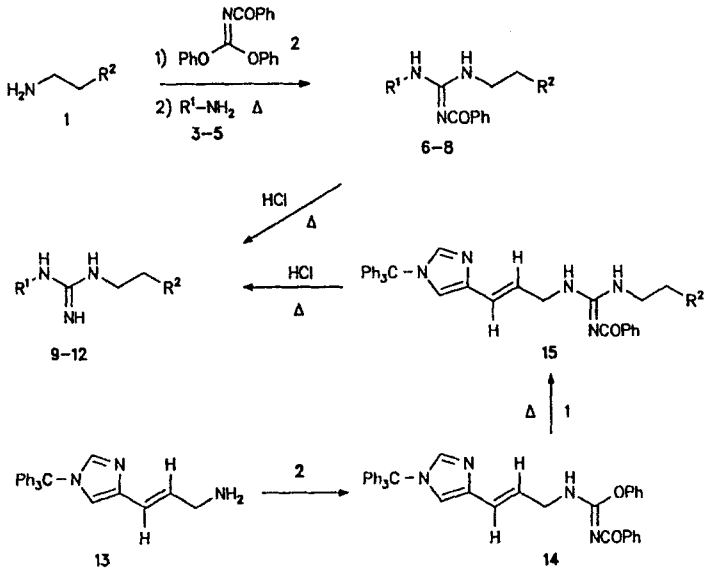
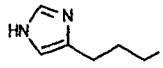
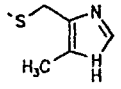
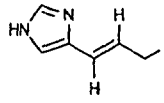
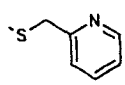
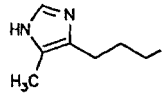
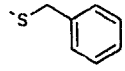
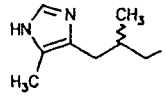
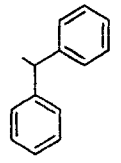


Compd. no.	R^1	1, 6–12, 15	R^2
3, 6, 9		a	
10		b	
4, 7, 11		c	
5, 8, 12		d	

Scheme 2

N-benzoyl isoureas with 3-(5-methyl-1*H*-imidazol-4-yl)propanamine (**4**) or racemic 3-(5-methyl-1*H*-imidazol-4-yl)-2-methylpropanamine (**5**)[26], respectively, and subsequent chromatographic purification of the resulting benzoyl guanidines **7b-d** and **8b-d**. Acidic hydrolysis afforded the corresponding guanidines **11b-d** and **12b-d** in almost quantitative yield. For the synthesis of **10b-d** the N^{τ}-protected (*E*)-configurated 3-(1*H*-imidazol-4-yl)allylamine **13**[26] was treated with **2**, followed by isolation of the crystalline isourea **14** and subsequent aminolysis with **1b-d**, chromatographic purification of **15b-d** and final hydrolysis. Yields, physical and spectroscopic data are given in tab. 1 and 2.

Pharmacological Results and Discussion

Guanidines **10-12** were screened for H_2-agonistic activity on the isolated spontaneously beating right guinea-pig atrium as well as for H_1-antagonistic properties[11,12] in the isolated guinea-pig ileum. Results together with lit. data for **9a-d** and for hydrophilic leads **10a**, **11a**, and **12a** are listed in tab. 3.

All new compounds display a significant decrease of H_2-agonistic activity compared with those analogues [**9a-d**] containing the classical 3-(1*H*-imidazol-4-yl)propyl substituent. This fact again emphasizes the outstanding efficacy-contributing properties of the "homohistamine"[4] fragment (**3**). A view into each group of compounds **10**, **11**, or **12**, respectively, reveals heterogeneous trends of structure-activity relationships. The activity of **11a** - which is more potent than **10a** as well as **12a** (potency: 24% relative to impromidine) - is not significantly altered by introduction of one of the three lipophilic substituents [**11b-d**]. Apparently the situation is similar for the analogues of **10a** (potency: 7% relative to impromidine) with the exception of **10c**. For all compounds mentioned so far full or nearly full agonism is observed (intrinsic activities 0.83-1.0). As far as the group of racemic **12a-d** is concerned, lipophilic substitution can obviously enhance both intrinsic activity and potency compared with **12a** which itself is merely a weak partial H_2-agonist (i.a. = 0.34). Especially the 3,3-diphenylpropyl substituent seems to exert a beneficial effect and partially compensates the loss of H_2-agonism observed when the homohistamine part of **9a** is formally methylated at C-5 of the imidazole nucleus and C-2 of the propyl chain (**9a** → **12a**).

These data confirm previous observations that the nature of the affinity-contributing moiety can apparently influence the intrinsic activity of guanidine-type H_2-agonists in a positive sense[4,5]. Taken together with the antagonistic activity at ileal H_1-receptors (-lg $K_B \approx 5$ - 6.7) the new guanidines **10b-d**, **11b-d**, and **12b-d** have to be regarded as weak or moderate H_2-agonists that do not display a pronounced preference for one of the histamine receptor subtypes concerning receptor subtype selectivity.

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Experimental Part

Chemistry

Melting points (uncorrected): Büchi appratus. Elemental analyses (C, H, N): Analytical department of the Institute of Pharmacy, Freie Universität Berlin.- Structures were confirmed by ^{1}H-NMR (Bruker WP 60 (60 MHz) or Bruker WM 250 (250 MHz), TMS) (see Tab. 2) and by mass spectrometry (EI: Finnigan MAT CH7A (170°C, 70 eV) or MAT 711 (200°C, 80 eV); FAB: Finnigan MAT CH5DF ($^+$FAB, xenon, DMSO/glycerol) (see Tab. 1).- Chromatographic separations: Chromatotron 7924T (Harrison Research), glass rotors with 4 mm layers of silica gel 60 PF_{254} containing gypsum (Merck).

General procedure for the synthesis of N-benzoyl guanidines **7b-d** *and* **8b-d**

A mixture of 5 mmol of **1b-d** and 5 mmol **2** is stirred in CH_2Cl_2 (20 ml) for 15 min at room temp. and smoothly evaporated to dryness. The crude isourea is dissolved in pyridine (30 ml), 5.5 mmol of **4** or **5** are added and the solution is refluxed for 1 h. After evaporation *in vacuo* the crude

Tab. 1: Preparative, analytical and mass spectrometric data

Compd.	yield (%)	mp. (°C) (solvent)	formula (molecular mass)	analyses calc: C	H	N	found: C	H	N	m/z[a] (% relative intensity)
7b	70	94 (EtOAc/Et_2O)	$C_{23}H_{28}N_6OS$ (436.6)	63.3	6.46	19.3	63.3	6.54	19.2	436 ($M^{+\cdot}$, 20), 341 (10), 125 (9), 109 (30), 96 (45), 95 (53), 93 (70), 77 (50)
7c	60	106 (EtOAc/Et_2O)	$C_{24}H_{29}N_5OS$ (435.6)	66.2	6.71	16.1	66.2	6.74	16.2	435 ($M^{+\cdot}$, 4), 344 (16), 123 (40), 109 (27), 105 (100), 96 (15), 95 (22), 91 (73), 77 (67), 65 (14)
7d	65	amorphous	$C_{30}H_{33}N_5O$ (479.6)	75.1	6.93	14.6	74.5	7.08	14.3	479 ($M^{+\cdot}$, 12), 312 (8), 167 (12), 109 (27), 105 (100), 95 (17), 77 (45)
8b	68	amorphous	$C_{24}H_{30}N_6OS$ (450.6)	64.0	6.71	18.7	63.7	6.92	18.2	450 ($M^{+\cdot}$, 8), 358 (9), 282 (28), 267 (6), 222 (6), 204 (8), 191 (6), 137 (12), 123 (30), 105 (100), 96 (14), 95 (19), 93 (53), 82 (17), 77 (24)
8c	73	amorphous	$C_{25}H_{31}N_5OS$ (449.6)	66.8	6.95	15.6	66.3	6.99	15.5	450 ($M^{+\cdot}$, 9), 359 (40), 335 (12), 327 (8), 204 (18), 137 (31), 123 (30),105 (100), 96 (13), 95 (20), 91 (52), 77 (39)
8d	75	amorphous	$C_{31}H_{35}N_5O$ (493.6)	75.4	7.15	14.2	75.6	7.11	14.0	493 ($M^{+\cdot}$, 7), 398 (11), 167 (17), 137 (12), 123 (28), 105 (100), 96 (22), 95 (27), 91 (8), 77 (60)
10b	>95	188-9 (H_2O)	$C_{15}H_{20}N_6S{\cdot}3C_6H_3N_3O_7$ (1003.7)	39.5	2.91	20.9	39.4	2.76	20.5	c)
10c	>95	110-13 (Me_2CO/Et_2O)	$C_{16}H_{21}N_5S{\cdot}2C_6H_3N_3O_7$ (773.6)	b)						316 ([M+H]$^+$, 67), 210 (51), 151 (16), 107 (30), 91 (100), 80 (14)
10d	>95	133-6 (Et_2O)	$C_{22}H_{25}N_5{\cdot}2C_6H_3N_3O_7$ (817.7)	b)						360 ([M+H]$^+$, 39), 254 (100), 167 (32), 165 (15), 107 (37), 100 (26), 91 (51)
11b	>95	208-10 (441.8)	$C_{16}H_{24}N_6S{\cdot}3HCl$ (EtOH)	43.5	6.16	19.0	43.5	6.16	18.8	333 ([M+H]$^+$, 100), 242 (13), 208 (5), 165 (7), 152 (4), 140 (9), 124 (44), 123 (67), 114 (10), 109 (18), 100 (13), 96 (23), 95 (22), 93 (48)
11c	>95	100-103 (H_2O)	$C_{17}H_{25}N_5S{\cdot}2C_6H_3N_3O_7$ $\cdot H_2O$ (807.7)	43.1	4.12	19.1	43.1	4.07	18.7	332 ([M+H]$^+$, 97), 242 (5), 165 (10), 151 (9), 123 (61), 109 (14), 96 (12), 95 (19), 91 (100)
11d	>95	amorphous	$C_{23}H_{29}N_5{\cdot}2HCl$ (448.4)	b)						376 ([M+H]$^+$, 100), 254 (14), 208 (4), 167 (26), 123 (76), 100 (30), 91 (28)
12b	>95	201-2 ($EtOH/Et_2O$)	$C_{17}H_{26}N_6S{\cdot}3HCl$ (455.9)	44.8	6.41	18.4	44.4	6.62	18.3	347 ([M+H]$^+$, 69), 256 (20), 137 (40), 124 (25), 123 (20), 100 (14), 96 (22), 95 (26), 93 (100)
12c	>95	amorphous	$C_{18}H_{27}N_5S{\cdot}2HCl$ (418.4)	b)						346 ([M+H]$^+$, 100), 137 (43), 123 (15), 100 (16), 96 (16), 95 (23), 91 (85)
12d	>95	214 (EtOH)	$C_{24}H_{31}N_5{\cdot}2HCl$ (462.5)	62.3	7.19	15.1	62.0	7.41	15.2	390 ([M+H]$^+$, 100), 294 (11), 254 (10), 167 (32), 165 (25), 154 (9), 152 (13), 137 (87), 123 (15), 117 (18), 115 (16), 104 (16), 100 (25), 96 (17), 95 (43), 91 (39)
14	85	108	$C_{39}H_{32}N_4O_2$ (588.7)	79.6	5.48	9.52	79.5	5.56	9.52	c)
15b	71	136-7 (Et_2O)	$C_{41}H_{38}N_6OS$ (662.8)	74.3	5.78	12.7	74.3	5.79	12.6	c)
15c	68	134-5 (Et_2O)	$C_{42}H_{39}N_5OS$ (661.9)	76.2	5.94	10.6	76.1	5.94	10.6	c)
15d	75	184 (EtOH)	$C_{48}H_{43}N_5O$ (705.9)	81.7	6.14	9.92	81.6	6.15	9.70	c)

a) $^+$FAB-MS except for **7** and **8** (EI-MS). b) Not determined, very hygroscopic. c) Not determined.

product is dissolved in 5% aqueous HCl and phenol is thoroughly extracted with ether. The acidic layer is alkalized with 10% aqueous NH_3 and crude **7b-d** and **8b-d** are extracted into CH_2Cl_2. After drying over Na_2SO_4 the solution is concentrated and the product is purified by Chromatotron ($CHCl_3$/MeOH 99/1 (v/v), NH_3 atmosphere). Compounds **7d**, **8b-d** are obtained as amorphous solids; **4b,c** are recrystallized from EtOAc/Et_2O.

General procedure for the synthesis of the guanidines **10b-d**, **11b-d**, *and* **12b-d**

1.2-1.5 mmol of the corresponding *N*-benzoyl guanidine **7**, **8**, or **15** is refluxed in 6 N-HCl (40 ml) under control by TLC. After completion of the hydrolysis the solution is cooled, extracted thoroughly with ether and repeatedly evaporated to dryness after addition of absol. ethanol to obtain an amor-

Tab. 2: ^{1}H-NMR data*)

Compd.	δ (ppm); *J* (Hz)
7b	1.91 (m, 2H, -CH_2-CH_2-CH_2-), 2.13 (s, 3H, Im-5-CH_3), 2.59 (m, 2H, CH_2), 2.8 (m, 2H, CH_2), 3.35 (br, 2H, -CH_2-NH-), 3.75 (br, 2H, -CH_2-NH-), 3.87 (s, 2H, Py-CH_2-S), 7.1-7.7 (m, 6H, aromat.), 8.2 (m, 2H, aromat.), 8.45 (m, 1H, aromat.), 10.4 (br, 1H[a)], Imidazol-NH)
7c	1.89 (m, 2H, -CH_2-CH_2-CH_2-), 2.12 (s, 3H, Im-5-CH_3), 2.6-2.8 (m, 4H, CH_2), 3.34 (br, 2H, -CH_2-NH-), 3.75 (m, 4H, Ph-CH_2-S, -CH_2-NH-)
7d	1.83 (m, 2H, -CH_2-CH_2-CH_2-), 2.12 (s, 3H, Im-5-CH_3), 2.2-2.8 (m, 4H, CH_2), 3,5 (br, 4H, -CH_2-NH-), 4.2 (t, J=7, 1H, CH), 6.9-7.6 (m, 14H, aromat.), 8.13 (m, 2H, aromat.)
8b	0.96 (d, J=3.5, 3H, CH_3), 2.1 (m, 4H, Im-5-CH_3, CH), 2.52 (m, 2H, Im-CH_2-), 2.8 (br, 2H, SCH_2), 2.95-3.88 (m, 6H, Py-CH_2-S, -CH_2-NH-), 7.15-8.65 (m, 10H, aromat.), 10.55 (br, 1H[a)], Imidazol-NH)
8c	0.95 (d, J=6, 3H, CH_3), 2.1 (m, 4H, Im-5-CH_3, CH), 2.55 (m, 4H, Im-CH_2-, SCH_2), 3.35 (m, 6H, -CH_2-NH-, Ph-CH_2-S), 7-8.2 (m, 11H, aromat.), 10.4 (br, 1H[a)], Imidazol-NH)
8d	0.93 (br, 3H, CH_3), 2.09 (m, 4H, Im-5-CH_3, CH), 2.48 (m, 4H, Im-CH_2-, CH_2), 2.95-3.65 (m, 4H, -CH_2-NH-), 4.05 (m, 1H, Diphenyl-CH), 7.15-7.55 (m, 14H, aromat.), 8.12 (m, 2H, aromat.), 10.6 (br, 1H[a)], Imidazol-NH)
10b	2.7 (m, 2H, SCH_2), 3.5 (m, 2H, -CH_2-NH-), 4.07 (m, 2H, -CH_2-NH-), 4.26 (s, 2H, Py-CH_2-), 6.56 (m, 2H, -CH=CH-), 7.7-7.95 (m, 1H, 1H, 2H[a)], Py-5-H, Im-5-H, C=NH_2^+), 8.06 (m, 1H[a)], 1H, -NH-CH_2-, Py-3-H), 8.26 (m, 1H[a)], -NH-CH_2-), 8.43 (m,1H, Py-4-H), 8,78 (m, 1H, Py-6-H), 9.14 (s, 1H, Im-2-H), 13.63 (br, 2H[a)], Imidazolium-NH)
10c	2.55 (m, 2H, SCH_2), 3.43 (m, 2H, -CH_2-NH-), 3.82 (s, 2H, Ph-CH_2-S), 4.06 (m, 2H, -CH_2-NH-), 6.55 (m, 2H, -CH=CH-), 7.25-7.45 (m, 5H, aromat.), 7.74 (s, 1H, Im-5-H), 7.77 (m, 2H[a)], C=NH_2^+), 8.0 (m, 1H[a)], -NH-CH_2-), 8.2 (m, 1H[a)], -NH-CH_2-), 9.13 (s, 1H, Im-2-H), 14.98 (br, 2H[a)], Imidazolium-NH)
10d	2.3 (m, 2H, CH_2), 3.08 (m, 2H, -CH_2-NH-), 4.03 (m, 2H, CH_2-NH-), 4.13 (t, J=8.5, CH), 6.5 (m, 2H, CH=CH-), 7.15-7.35 (m, 10H, aromat.), 7.65 (s, 2H[a)], C=NH_2^+), 7,73 (s, 1H, Im-5-H), 8.12 (m, 2H[a)], -NH-CH_2-), 9.13 (s, 1H, Im-2-H), 14.9 (br, 2H[a)], Imidazolium-NH)
11b	1.83 (m, 2H, -CH_2-CH_2-CH_2-), 2.25 (s, 3H, Im-5-CH_3), 2.69 (m, 4H, SCH_2, Im-CH_2-), 3.17 (m, 2H, -CH_2-NH-), 3.46 (m, 2H, -CH_2-NH-), 4.31 (s, 2H, Py-CH_2-), 7.75 (s, 2H[a)], C=NH_2^+), 8.84 (d, J=5.5, 1H, Py-6-H), 8.52 (m, 1H, Py-4-H), 7.89-8.0 (m, 2H, Py-5-H, NH), 8.15 (m, 1H, 1H[a)], Py-3-H, NH), 8.97 (s, 1H, Im-2-H), 14.6 (br, 2H[a)], Imidazolium-NH)
11c	1.84 (m, 2H, -CH_2-CH_2-CH_2-), 2.24 (s, 3H, Im-5-CH_3), 2.54 (m, 2H, Im-CH_2-), 2.7 (t, J=7.5, 2H, SCH_2), 3.19 (m, 2H, -CH_2-NH-), 3.45 (m, 2H, CH_2), 3.83 (s, 2H, Ph-CH_2-), 7.2-7.4 (m, 5H, aromat.), 7.73 (s, 2H[a)], C=NH_2^+), 7.96 (m, 1H[a)], -NH-CH_2-), 8.22 (m, 1H[a)], -NH-CH_2-), 9.02 (s, 1H, Im-2-H)
11d	1.8 (m, 2H, -CH_2-CH_2-CH_2), 2.23 (s, 3H, Im-5-CH_3), 2.34-2.77 (m, 4H, CH_2), 3.07 (m, 4H, -CH_2-NH-), 4.1 (t, J=5, 1H, CH), 7.3 (m, 10H, aromat.), 7.5 (s, 2H[a)], C=NH_2^+), 8.09 (m, 2H[a)], -NH-CH_2-), 8.92 (s, 1H, Im-2-H),
12b	0.85 (d, J=6.5, 3H, CH_3), 2.09 (m, 1H, CH), 2.24 (s, 3H, Im-5-CH_3), 2.45-2.85 (m, 4H, CH_2), 3.05-3.55 (m, 4H, -CH_2-NH-), 4.27 (s, 2H, Py-CH_2-), 7.75 (s, 2H[a)], C=NH_2^+), 7.86 (m, 1H, Py-5-H), 8.09 (m, 1H, 1H[a)], Py-3-H, NH), 8.21 (s, 1H[a)], -NH-CH_2-), 8.45 (m, 1H, Py-4-H), 8.8 (d, J=5.5, Py-6-H), 8.96 (s, 1H, Im-2-H), 14.54 (br, 2H[a)], Imidazolium-NH)
12c	0.85 (d, J=6.5, 3H, CH_3), 2.09 (m, 1H, CH), 2.23 (s, 3H, Im-5-CH_3), 2.45-2.85 (m, 4H, CH_2), 3.05-3.25 (m, 2H, -CH_2-NH-), 3.43 (m, 2H, -CH_2-NH-), 3.83 (s, 2H, Ph-CH_2-), 7.24-7.39 (m, 5H, aromat.), 7.72 (s, 2H[a)], C=NH_2^+), 7.96 (m, 1H[a)], -NH-CH_2-), 8.18 (m, 1H[a)], -NH-CH_2-), 8.96 (s, 1H, Im-2-H), 14.5 (br, 2H[a)], Imidazolium-NH)
12d	0.84 (d, J=6.5, CH_3), 2.06 (m, 1H, CH), 2.23 (s, 3H, Im-5-CH_3), 2.29 (m, 2H, CH_2), 2.45-2.85 (m, 2H, CH_2), 3.02-3.26 (m, 4H, -CH_2-NH-), 4.19 (t, J=8,5, Diphenyl-CH), 7.18-7.32 (m, 12H, aromat., C=NH_2^+), 7.62 (s, 1H[a)], -NH-CH_2-), 8.11 (s, 1H[a)], -NH-CH_2-), 14,5 (br, 2H[a)], Imidazolium-NH)
14	4.29 (m, 2H, CH_2), 6.47-6.49 (m, 2H, -CH=CH-), 6,79 (s, 1H, Im-5-H), 7.13-7.92 (m, 18H, aromat.), 10.26 (m, 1H[a)], NH)
15b	2.75 (t, J=6.5, 2H, SCH_2), 3.67 (br, 2H, -CH_2-NH-), 3.81 (s, 2H, Py-CH_2-S), 4.1 (br. 2H, -CH_2-NH-), 6.35-6.53 (m, 2H, -CH=CH-), 6.77 (s, 1H, Im-5-H), 7.1-7.5 (m, 18H, aromat.), 7.62 (m, 1H, aromat.), 8.22 (m, 2H, aromat.), 8.5 (m, 1H, aromat.)
15c	2.66 (t, J=6.5, 2H, SCH_2), 3.6 (br. 2H, -CH_2-NH-), 3.66 (s, 2H, Ph-CH_2-S), 4.0 (br, 2H, -CH_2-NH-), 6.38 (dt, J=16/5, 1H, =CH-CH_2-), 6.5 (d, J=16, 1H, Im-CH=CH-), 6.77 (s, 1H, Im-5-H), 7.1-7.45 (m, 19H, aromat.), 8.18 (m, 2H, aromat.), 10.5 (br, 1H[a)], Imidazol-NH)
15d	2.4 (m, 2H, CH_2), 3.4 (br, 2H, -CH_2-NH), 4.0 (br, 3H, CH, -CH_2-NH-), 6.33 (dt, J=16/5, 1H, =CH-CH_2-), 6.44 (d, J=16, 1H, Im-CH=CH-), 6.77 (s, 1H, Im-5-H), 7.1-7.45 (m, 14H, aromat.), 8.17 (m, 2H, aromat.)

*) Bruker WM 250 (250 MHz) except data for **7d** and **11d** (Bruker WP 60 (60 MHz)). Solvent: $CDCl_3$ (**7, 8,14, 15**) or [D_6]DMSO (**10, 11, 12**). Abbreviations: br = broad, Im = imidazole, Ph = phenyl, Py = pyridyl. a) Exchangeable with D_2O.

phous solid or dry foam. Non stable or very hygroscopic hydrochlorides are converted into di- or tri-picrates for analysis. Compounds that gave even very hygroscopic picrates were characterized only by spectral methods.

N-Benzoyl-N'-[3-(1-triphenylmethyl-1H-imidazol-4-yl)-2-propen-1-yl]-O-phenylisourea (**14**)

A mixture of 30 mmol **13** and 30 mmol **2** is stirred in CH_2Cl_2 (70 ml) for 15 min at room temp. and smoothly evaporated to dryness. The residue is crystallized from ethanol.

General procedure for the synthesis of N-benzoyl guanidines **15b-d**

A solution of 5 mmol **14** and 5.5 mmol **1b-d** is refluxed in pyridine (40 ml) for 1 h. After evaporation of the solvent **15d** is crystallized directly from ethanolic solution. For the isolation of **15b,c** the residue is suspended in 5% aqueous HCl and extracted with ether. The acidic layer is alkalized with 25% aqueous NH_3 and crude **15b,c** are extracted into CH_2Cl_2. After drying over Na_2SO_4 the solution is evaporated and the product is purified by Chromatotron ($CHCl_3$/MeOH 99/1 (v/v), NH_3 atmosphere). Finally **15b,c** are crystallized from ether.

Tab. 3: Biological data

	atrium (H_2)			ileum (H_1)	
compound	i. a.[a] (±0.05)	pD_2[b] (±0.10)	rel. pot.[c] (%)	pA_2[d] (±0.10)	Ref.
histamine	1.0	6.00	100	-	
arpromidine	1.0	8.01	10230	7.7	[12]
9a (impromidine)	1.0	7.68	4810	5.5	[1]
9b	1.0	7.30	2000	5.4	[11]
9c	1.0		1260	5.3	[20]
9d	1.0	7.20	1580	6.3	[11]
10a	0.91	6.54	350	4.7	[4]
10b	0.83	6.16	140	5.0	
10c	0.86	5.48	30	5.6	
10d	0.85	6.23	170	6.6	
11a	0.90	7.06	1150	-	[4]
11a	0.85		810	-	[3]
11b	0.86	6.88	760	5.2	
11c	0.89	6.58	380	5.7	
11d	1.0	6.77	590	6.7	
12a	0.34	-	-	5.8	[4]
12b	0.35	-	-	5.9	
12c	0.60	5.09	10	6.7	
12d	0.90	6.21	160	6.6	

a) Intrinsic activity; mean of 3-4 experiments (± s.e.m.). b) Mean of 3-4 experiments (± s.e.m.).
c) Relative potency compared to histamine (=100%). d) Mean of 4 experiments (± s.e.m.).

Pharmacology

H_2-Agonism on the isolated guinea-pig atrium[27]

Male guinea-pigs (350-500 g) were sacrificed by a blow on the head and exsanguinated. The right atrium was rapidly removed, cleared of connective tissue, attached to a tissue holder in a 20 ml organ bath (32.5°C) containing *McEvans* solution[27] and aerated with carbogen. The pD_2 values and intrinsic activities were determined from isometrically recorded cumulative concentration-response curves[28] as described by *Lennartz* et al.[29], using histamine as the reference agonist (0.1-10 µM). Potential agonists were used as hydrochlorides. The maximum effect of the agonist studied was completely abolished by 10-30 µM cimetidine. H_2-receptor selectivity was verified by some experiments in the presence of 1 µM metoprolol.

H_1-antagonistic activity on the isolated guinea-pig ileum

The H_1-antagonistic activity was determined from isotonically recorded (preload 0.5 g) cumulative concentration-response curves, as described[29], using 20 ml organ baths containing Tyrode solution aerated with carbogen at 37°C. Hydrochlorides were tested at concentrations of 0.3-30 µM versus histamine after 10 min of incubation. Apparent -lg K_B values were calculated from the rightward shift of the histamine curve in the presence and absence of antagonist[28].

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