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Synthesis and histamine H_2 agonistic activity of arpromidine analogues: replacement of the pheniramine-like moiety by non-heterocyclic groups*

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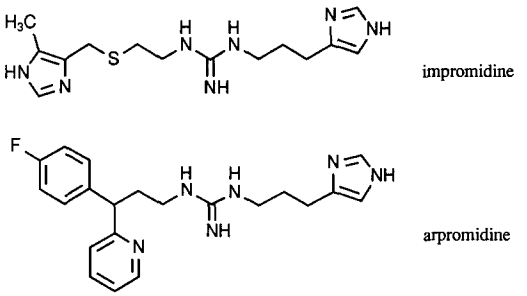
Summary — Analogues of the potent histamine H_2 agonist arpromidine, characterized by non-heterocyclic groups (phenyl, cyclohexyl, alkyl) instead of the pheniramine-like portion, were prepared and tested for their H_2 agonistic and H_1 antagonistic activity in the isolated guinea pig right atrium and ileum, respectively. In the diphenylpropylguanidine series an increase in H_2 agonistic potency resulted from mono- or difluorination at one or both phenyl rings in the *meta* and/or *para* position ($pD_2 \leq 7.75$ *vs* $pD_2 = 7.15$ for the unsubstituted parent compound). Compounds chlorinated at both phenyl rings were considerably less potent. Highest combined H_2 agonistic/H_1 antagonistic potency was found in the 4-fluorophenyl series. The arpromidine analogue with cyclohexyl and methyl group instead of phenyl and pyridine ring proved to be 30 times more potent than histamine in the atrium. The H_1 antagonistic potency in cyclohexyl compounds was lower than in the diaryl series. Thus, aromatic rings appear not to be required for high H_2 agonistic potency but are useful for combined H_2 agonistic/H_1 antagonistic activity.

histamine / H_2 receptor / H_2 agonist / arpromidine / impromidine / H_1 antagonist / antihistamine

Introduction

The synthesis of the potent and selective histamine H_2 agonist impromidine [1, 2] (scheme 1) has stimulated the search for further guanidine-type H_2 histaminergic compounds both as regards theoretical considerations and the development of future drugs. For example, as demonstrated by using impromidine in severely ill patients, agonism on cardiovascular H_2 receptors may be a promising new approach superior to conventional therapy with sympathomimetics in the acute treatment of end-stage heart failure [3]. The 'affinity-conferring' cimetidine-like 2-[(5-methyl-imidazol-4-yl)methylthio]-ethyl portion in impromidine has been replaced by a large number of various substructures chemically derived from other H_2 antagonists or by H_2 non-specific groups (for recent reviews see [4, 5]). The incorporation of a pheniramine-like moiety resulted in arpromidine [6, 7] which may be considered a new chemical lead for the development of cardiohistaminergics [4, 8–10]. Arpromidine, a pharmacological hybrid, is about 100 times more potent than histamine as an H_2 agonist in the guinea pig right atrium and an H_1 antagonist which is about equipotent with pheniramine. Some diphenylpropylguanidine analogues of arpromidine are known to produce a similar dual mode of action but at a lower level of potency [6, 7, 11]. However, structure–activity relationships have not been studied in more detail regarding their similarities to arpromidine-like compounds, *eg* the influence of multiple ring halogenation (F, Cl) that was found to be very effective in the arpromidine series.



Scheme 1.

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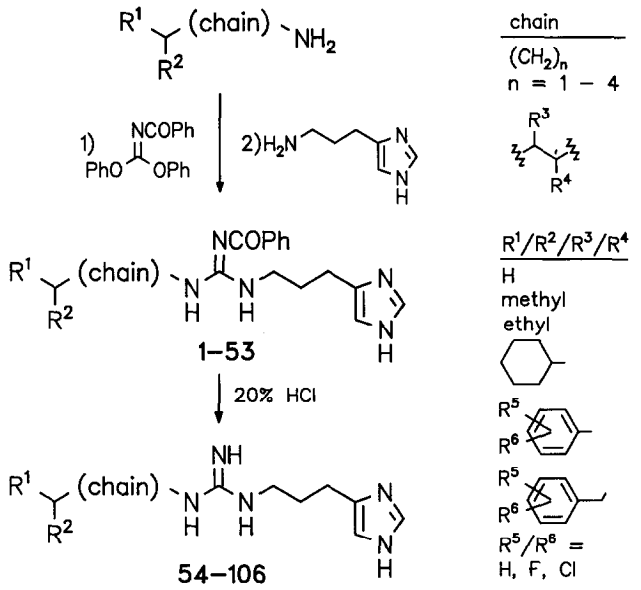
The aim of the present paper was to investigate the contribution to H_2 agonistic potency of non-heterocyclic groups such as unsubstituted or halogenated phenyl, cyclohexyl, or alkyl groups instead of the pyridyl and/or the phenyl group in arpromidine. Moreover, the connecting chain was modified concerning length, branching and arrangement of the aromatic rings, respectively.

Chemistry

For the synthesis of the guanidines **54–106** diphenyl benzoylcarbonimidate [12] was first allowed to react with appropriate primary amines at ambient temperature (scheme 2). The phenylisoureas formed were directly treated with 3-(imidazol-4-yl)propanamine [13] under reflux in pyridine and, finally, the benzoylguanidines **1–53** were hydrolyzed under acidic conditions. The requisite amines not commercially available were prepared according to the synthetic pathways I–V outlined in scheme 3.

Results and discussion

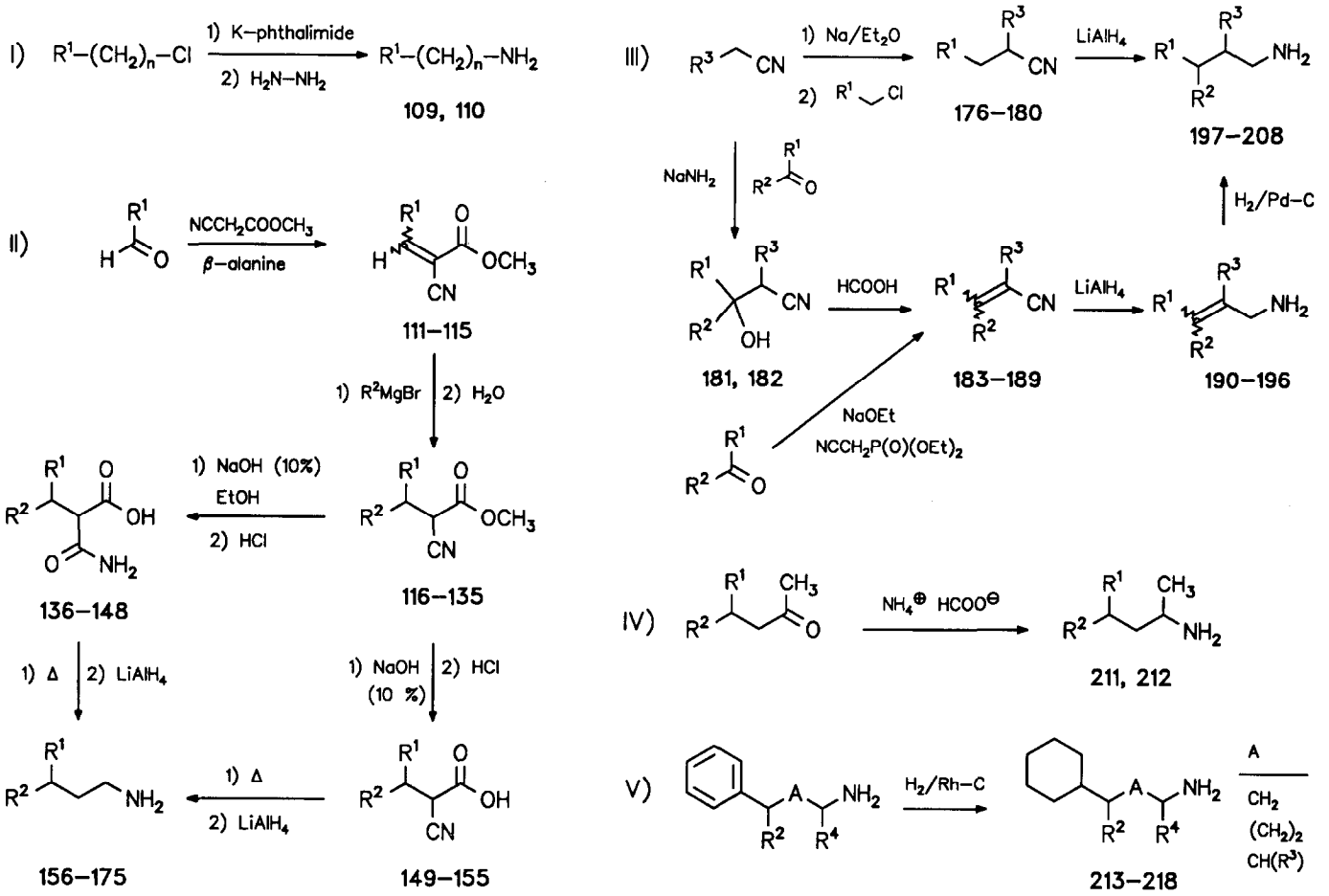
The H_2 agonistic activity of the guanidines **54–106** was determined in the isolated spontaneously beating guinea pig right atrium (positive chronotropic response). All compounds were also tested for H_1 antagonism in the isolated guinea pig ileum. Additionally, the hemodynamic profile of the



Scheme 2.

guanidines **56, 64** and **65** was investigated in isolated perfused guinea pig hearts (Langendorff technique) *versus* impromidine. All pharmacological experiments were performed with the dihydrochlorides of the guanidines **54–106**. The results are summarized in tables I–IV.

All compounds tested proved to be full or nearly full H_2 agonists (intrinsic activity 0.8–1.0) in the atrium with potencies ranging from $pD_2 = 5.0$ (**88**) to 7.75 (**65, 71**) corresponding to about 0.1 and 40 times the activity of histamine. In the phenylalkylguanidine series (**55–62**) the highest potency is found in compounds with 3- and 4-membered carbon chain. However, there is clear evidence that an aromatic ring is not required at all. The cyclohexyl analogues **95–97** are about equipotent with **56, 57** and **59**. Moreover, a small alkyl group also appears to contribute to the H_2 receptor affinity. Compound **54** characterized by an isopentyl substituent at the guanidine system is slightly more active than histamine and there is about a 6-fold increase in potency resulting from an additional methyl substituent both in the phenyl and in the cyclohexyl series (**59, 97**). The positive influence of methyl is even higher than that of a second phenyl or cyclohexyl ring as in **64** or **98**. The impact of halogen substitution on H_2 agonistic activity seems to be contrary in monoaryl and in diarylalkyl compounds. For example substitution with fluorine in *para* position of **59** results in a rather slight decrease (see **61, 62**), whereas the analogues of **64** fluorinated at one or both phenyl rings are up to 3 times more potent than the respective parent compound. So far, these results agree fairly well with findings on the benzylthioalkylguanidines [14] and the arpromidine series [6]. It was speculated in a recent QSAR study that in contrast to monoaryl compounds, the second aromatic ring in diarylalkylguanidines such as arpromidine or **65** places the substituted phenyl ring in a position so that interactions of substituents with the binding site become favourable (Franke R, Buschauer A, submitted for publication). However, contrary to the arpromidine series the positive substituent effect is only found in fluorinated analogues of **64**, such as **65–67, 71–73, 77, 78** and **81**. The corresponding chlorinated substances – except **70** – are about equipotent with the parent compound **64** or up to 100 times less active. The imidazolylpropylguanidine moiety in guanidine-type H_2 agonists is considered essential in eliciting a biological response [2]. Recently, a gene encoding the canine histamine H_2 receptor has been cloned [15]. It is conceivable that the imidazole ring is bound to an H-bonding region in the putative fifth transmembrane helix (Asp and Thr) of the receptor protein and that the guanidinium cation interacts with a negatively charged group in the third helix (Asp). Presumably, the contribution of the phenylalkyl or



Scheme 3.

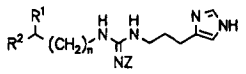
diphenylalkyl substituents consists of providing additional binding by interacting with an accessory binding site [4]. Possibly, fluorine atoms are more favourable substituents than chlorine atoms owing to the formation of electron donor–acceptor complexes, dipol–dipol or dipol–ion interactions, respectively. Nevertheless, in the case of chloro compounds steric factors might also play a role in lower affinity, and it cannot be excluded that the lipophilicity of the chloro compounds is beyond the optimum in the diphenylalkylguanidine series rather than in arpromidine-like substances.

Compounds with 2,3- or 3,4-diarylalkyl groups, such as **89–94**, are considerably less potent in the atrium than 3,3-diarylpropylguanidines. Obviously, the distance between the guanidino group and aromatic rings should be 3 carbon atoms, as also found in the arpromidine series [6]. In contrast to H_2 agonists of the imidazole or pyridine series [16, 17] most of the substances chain-branched α to the guanidine system (R^4 = Me), *eg* **99–101**, **105** (table III), are less potent than the corresponding non-branched compounds. The influence of a β-methyl group (R^3 = Me) is less pronounced.

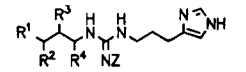
Concerning both H_2 agonism and H_1 antagonism the fluorinated compounds proved to be the optimum, the antagonist activity in the ileum achieving up to pK_B = 7.45 corresponding to about half the potency of pheniramine.

In isolated perfused guinea pig hearts arpromidine and its phenyl analogue **65** produce about the same maximal increase in contractility as impromidine (table IV). However, comparing ED_{50} values, arpromidine and **65** are about 1.5 and 1.2 times more potent than the reference compound. By contrast, the diphenylpropylguanidine **64** is only a partial agonist

Table I. Structures and analytical data of the new benzoylguanidines and corresponding guanidines.



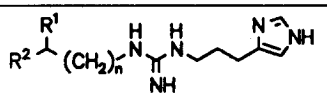
			Benzoylguanidines **1 - 45**: Z = COPh			Guanidines **54 - 98**: Z = H			
R¹	R²	n	No.	Mp[a] (°C)	Molecular formula[b] Anal (C, H, N)	EI-MS (m/z)[c] (% rel. int.)	No.	Mp[d] (°C)	Molecular formula[b] Anal (C, H, N)	FAB-MS / [EI-MS] (m/z)[e] (% rel. int.)
Me	Me	2	**1**	130[f]	$C_{19}H_{27}N_5O$	341 (2)	**54**	133	$C_{13}H_{25}N_5 \cdot 2C_6H_3N_3O_7 \cdot H_2O$	252 (<1), 238 (100)
Ph	H	1	**2**	153	$C_{22}H_{25}N_5O$	375 (15)	**55**	137	$C_{15}H_{21}N_5 \cdot 2C_6H_3N_3O_7 \cdot H_2O$	272 (100), 109 (96)
Ph	H	2	**3**	146[f]	$C_{23}H_{27}N_5O$	389 (1)	**56**	86	$C_{16}H_{23}N_5 \cdot 2C_6H_3N_3O_7 \cdot H_2O$	286 (100), 109 (86)
Ph	H	3	**4**	132[f]	$C_{24}H_{29}N_5O$	403 (3)	**57**	147	$C_{17}H_{25}N_5 \cdot 2C_6H_3N_3O_7 \cdot H_2O$	300 (100), 109 (83)
Ph	H	4	**5**	126	$C_{25}H_{31}N_5O$	417 (9)	**58**	125	$C_{18}H_{27}N_5 \cdot 2C_6H_3N_3O_7$	314 (100), 109 (87)
Ph	Me	2	**6**	111[f]	$C_{24}H_{29}N_5O$	403 (7)	**59**	140	$C_{17}H_{25}N_5 \cdot 2C_6H_3N_3O_7$	328 (67), 109 (100)
Ph	Et	2	**7**	109	$C_{25}H_{31}N_5O$	417 (15)	**60**	145	$C_{18}H_{27}N_5 \cdot 2C_6H_3N_3O_7$	314 (88), 91 (100)
4-FC_6H_4	Me	2	**8**	110	$C_{24}H_{28}FN_5O$	421 (6)	**61**	140	$C_{17}H_{24}FN_5 \cdot 2C_6H_3N_3O_7$	318 (100), 109 (95)
4-FC_6H_4	Et	2	**9**	102[f]	$C_{25}H_{30}FN_5O$	435 (15)	**62**	140	$C_{18}H_{26}FN_5 \cdot 2C_6H_3N_3O_7$	332 (53), 109 (100)
Ph	Ph	1	**10**	132	$C_{28}H_{29}N_5O$	451 (5)	**63**	175	$C_{21}H_{25}N_5 \cdot 2C_6H_3N_3O_7$	348 (40), 109 (100)
Ph	3-FC_6H_4	2	**13**	131	$C_{29}H_{30}FN_5O$	483 (2)	**66**	141	$C_{22}H_{26}FN_5 \cdot 2C_6H_3N_3O_7$	380 (49), 109 (100)
Ph	3,4-$F_2C_6H_3$	2	**14**	131	$C_{29}H_{29}F_2N_5O$	501 (1)	**67**	147	$C_{22}H_{25}F_2N_5 \cdot 2C_6H_3N_3O_7 \cdot H_2O$	398 (36), 109 (100)
Ph	3-ClC_6H_4	2	**16**	116[f]	$C_{29}H_{30}ClN_5O$	499 (1)	**69**	170	$C_{22}H_{26}ClN_5 \cdot 2C_6H_3N_3O_7$	396 (43), 109 (100)
4-FC_6H_4	3-FC_6H_4	2	**19**	125	$C_{29}H_{29}F_2N_5O \cdot H_2O$	501 (5)	**72**	147	$C_{22}H_{25}F_2N_5 \cdot 2C_6H_3N_3O_7 \cdot H_2O$	398 (48), 109 (100)
4-FC_6H_4	3,4-$F_2C_6H_3$	2	**20**	157[g]	$C_{29}H_{28}F_3N_5O$	519 (29)	**73**	137	$C_{22}H_{24}F_3N_5 \cdot 2C_6H_3N_3O_7$	416 (46), 109 (100)
4-FC_6H_4	4-ClC_6H_4	2	**21**	161	$C_{29}H_{29}ClFN_5O$	517 (5)	**74**	154	$C_{22}H_{25}ClFN_5 \cdot 2C_6H_3N_3O_7 \cdot {}^1/_2H_2O$	414 (16), 109 (100)
4-FC_6H_4	3,4-$Cl_2C_6H_3$	2	**23**	141[f]	$C_{29}H_{28}Cl_2FN_5O$	551 (8)	**76**	165	$C_{22}H_{24}Cl_2FN_5 \cdot 2C_6H_3N_3O_7$	448 (81), 109 (100)
3-FC_6H_4	3-FC_6H_4	2	**24**	137	$C_{29}H_{29}F_2N_5O$	501 (<1)	**77**	173	$C_{22}H_{25}F_2N_5 \cdot 2C_6H_3N_3O_7 \cdot H_2O$	398 (53), 109 (100)
3-FC_6H_4	3,4-$F_2C_6H_3$	2	**25**	128	$C_{29}H_{28}F_3N_5O$	519 (4)	**78**	160	$C_{22}H_{24}F_3N_5 \cdot 2C_6H_3N_3O_7$	416 (22), 109 (100)
3-FC_6H_4	4-ClC_6H_4	2	**26**	144[f]	$C_{29}H_{29}ClFN_5O \cdot H_2O$	517 (1)	**79**	134	$C_{22}H_{25}ClFN_5 \cdot 2C_6H_3N_3O_7$	414 (15), 109 (100)
3-FC_6H_4	3-ClC_6H_4	2	**27**	[h]	$C_{29}H_{29}ClFN_5O \cdot 1{}^1/_2H_2O$	517 (2)	**80**	178	$C_{22}H_{25}ClFN_5 \cdot 2C_6H_3N_3O_7$	414 (32), 109 (100)
3,4-$F_2C_6H_3$	3,4-$F_2C_6H_3$	2	**28**	155[i]	$C_{29}H_{27}F_4N_5O$	537 (9)	**81**	170	$C_{22}H_{23}F_4N_5 \cdot 2C_6H_3N_3O_7$	434 (17), 109 (100)
3,4-$F_2C_6H_3$	4-ClC_6H_4	2	**29**	158	$C_{29}H_{28}ClF_2N_5O$	535 (1)	**82**	134	$C_{22}H_{24}ClF_2N_5 \cdot 2C_6H_3N_3O_7$	432 (38), 109 (100)
3,4-$F_2C_6H_3$	3-ClC_6H_4	2	**30**	123	$C_{29}H_{28}ClF_2N_5O$	535 (4)	**83**	164	$C_{22}H_{24}ClF_2N_5 \cdot 2C_6H_3N_3O_7 \cdot H_2O$	432 (26), 109 (100)
4-ClC_6H_4	4-ClC_6H_4	2	**31**	148	$C_{29}H_{29}Cl_2N_5O$	533 (2)	**84**	173	$C_{22}H_{25}Cl_2N_5 \cdot 2C_6H_3N_3O_7 \cdot H_2O$	430 (18), 109 (100)
3-ClC_6H_4	3-ClC_6H_4	2	**34**	128	$C_{29}H_{29}Cl_2N_5O$	533 (3)	**87**	190-5	$C_{22}H_{25}Cl_2N_5 \cdot 2C_6H_3N_3O_7$	430 (25), 109 (100)
3-ClC_6H_4	3,4-$Cl_2C_6H_3$	2	**35**	135[i]	$C_{29}H_{28}Cl_3N_5O$	567 (2)	**88**	182	$C_{22}H_{24}Cl_3N_5 \cdot 2C_6H_3N_3O_7 \cdot H_2O$	464 (17), 109 (100)
4-FC_6H_4	4-$FC_6H_4CH_2$	1	**36**	[h]	$(C_{29}H_{29}F_2N_5O)$	501 (2)	**89**	155-6	$C_{22}H_{25}F_2N_5 \cdot 2C_6H_3N_3O_7 \cdot {}^1/_2H_2O$	398 (21), 109 (100)
4-FC_6H_4	3-$FC_6H_4CH_2$	1	**37**	[h]	$(C_{29}H_{29}F_2N_5O)$	501 (4)	**90**	166	$C_{22}H_{25}F_2N_5 \cdot 2C_6H_3N_3O_7$	398 (71), 109 (100)
4-FC_6H_4	4-$ClC_6H_4CH_2$	1	**38**	[h]	$(C_{29}H_{29}ClFN_5O)$	517 (2)	**91**	176	$C_{22}H_{25}ClFN_5 \cdot 2C_6H_3N_3O_7$	414 (35), 109 (100)
4-ClC_6H_4	3-$FC_6H_4CH_2$	1	**39**	125[j]	$C_{29}H_{29}ClFN_5O$	517 (<1)	**92**	169-75	$C_{22}H_{25}ClFN_5 \cdot 2C_6H_3N_3O_7 \cdot H_2O$	414 (22), 109 (100)
4-ClC_6H_4	4-$ClC_6H_4CH_2$	1	**40**	[h]	$(C_{29}H_{29}Cl_2N_5O)$	533 (3)	**93**	192	$C_{22}H_{25}Cl_2N_5 \cdot 2C_6H_3N_3O_7$	430 (47), 109 (100)
c-Hex	H	2	**42**	147	$C_{23}H_{33}N_5O$	395 (10)	**95**	141	$C_{16}H_{29}N_5 \cdot 2C_6H_3N_3O_7$	[291 (1), 44 (100)]
c-Hex	H	3	**43**	138	$C_{24}H_{35}N_5O$	409 (88)	**96**	169	$C_{17}H_{31}N_5 \cdot 2C_6H_3N_3O_7 \cdot {}^1/_2H_2O$	[305 (47), 224 (100)]
c-Hex	Me	2	**44**	126	$C_{24}H_{35}N_5O$	409 (19)	**97**	138	$C_{17}H_{31}N_5 \cdot 2C_6H_3N_3O_7$	306 (40), 109 (100)
c-Hex	c-Hex	2	**45**	177	$C_{29}H_{43}N_5O$	477 (21)	**98**	169	$C_{22}H_{39}N_5 \cdot 2C_6H_3N_3O_7 \cdot {}^1/_2H_2O$	[373 (2), 83 (100)]

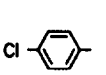
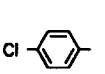
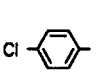


				Benzoylguanidines **46 - 53**: Z = COPh				Guanidines **99 - 106**: Z = H		
R¹	R²	R³	R⁴	No.	Mp[a] (°C)	Molecular formula[b] Anal (C, H, N)	EI-MS (m/z)[c] (% rel. int.)	No.	Mp[d] (°C)	Molecular formula[b] Anal (C, H, N)	FAB-MS / [EI-MS] (m/z)[e] (% rel. int.)
Ph	H	H	Me	**46**	110[e]	$C_{24}H_{29}N_5O$	403 (5)	**99**	147	$C_{17}H_{25}N_5 \cdot 2C_6H_3N_3O_7 \cdot H_2O$	300 (56), 109 (100)
c-Hex	H	H	Me	**47**	[h]	$(C_{24}H_{35}N_5O)$	409 (13)	**100**	104	$C_{17}H_{31}N_5 \cdot 2C_6H_3N_3O_7$	306 (<1), 109 (100)
c-Hex	c-Hex	H	Me	**48**	[h]	$(C_{30}H_{45}N_5O)$	491 (12)	**101**	171	$C_{23}H_{41}N_5 \cdot 2C_6H_3N_3O_7$	[387 (<1), 44 (100)]
c-Hex	c-Hex	Me	H	**49**	130[f]	$C_{28}H_{29}N_5O$	491 (2)	**102**	183	$C_{23}H_{41}N_5 \cdot 2C_6H_3N_3O_7$	[387 (3), 306 (100)]
Ph	Ph	H	Me	**50**	[h]	$C_{30}H_{33}N_5O$	479 (4)	**103**	122	$C_{23}H_{29}N_5 \cdot 2C_6H_3N_3O_7$	[375 (57), 114 (100)]
Ph	Ph	Me	H	**51**	140	$C_{30}H_{33}N_5O$	479 (3)	**104**	172	$C_{23}H_{29}N_5 \cdot 2C_6H_3N_3O_7$	[375 (43), 167 (100)]
4-FC_6H_4	4-FC_6H_4	H	Me	**52**	81[j]	$C_{30}H_{31}F_2N_5O \cdot {}^1/_2H_2O$	516[k] (3)	**105**	117	$C_{23}H_{27}F_2N_5 \cdot 2C_6H_3N_3O_7 \cdot H_2O$	[411 (6), 203 (100)]
4-FC_6H_4	4-FC_6H_4	Me	H	**53**	185	$C_{30}H_{31}F_2N_5O$	515 (7)	**106**	158	$C_{23}H_{27}F_2N_5 \cdot 2C_6H_3N_3O_7$	[411 (27), 203 (100)]

[a]Recrystallized from MeCN unless otherwise indicated. [b]All compounds analyzed for C, H, N, except formulas in parentheses. [c]$M^{+\cdot}$, base peak: m/z = 105. [d]All picrates recrystallized from EtOH – H_2O. [e]$[M + H]^+$ (FAB) or $M^{+\cdot}$ (EI, in square brackets) and base peak. [f]From EtOAc. [g]From MeCN – Et_2O. [h]Hygroscopic amorphous solids. [i]From EtOAc – Et_2O. [j]From CH_2Cl_2. [k]FAB-MS: $[M + H]^+$.

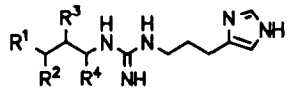
Table II. H_2 agonistic and H_1 antagonistic activity of phenyl and cyclohexylalkylguanidines **54–98** in guinea pig atrium and ileum.



Compd.	R^1	R^2	n	Atrium[a] i. a.	Atrium[a] pD_2 ± 0.1	Ileum[b] pK_B ± 0.2
histamine				1.0	6.0	-
impromidine[c]				1.0	7.7[d]	5.5[d]
arpromidine[d]				1.0	8.0	7.65
54	Me	Me	2	0.9	6.20	4.60
55	Ph	H	1	0.8	5.80	5.55
56	Ph	H	2	1.0	6.70	6.15
57	Ph	H	3	1.0	6.70	6.10
58	Ph	H	4	0.9	6.00	6.75
59	Ph	Me	2	1.0	7.50	5.60
60	Ph	Et	2	1.0	7.30	6.15
61	4-FPh	Me	2	1.0	7.35	6.00
62	4-FPh	Et	2	1.0	7.20	6.50
63	Ph	Ph	1	0.8	6.20	6.15
64	Ph	Ph	2	1.0	7.15[e]	7.05[f]
65[d]			2	1.0	7.75	7.45
66			2	1.0	7.35	6.45
67			2	1.0	7.30	7.00
68[d]			2	1.0	7.10	7.00
69			2	0.9	6.30	5.55
70[d]			2	1.0	7.45	6.70
71			2	1.0	7.75	7.35
72			2	1.0	7.45	7.45
73			2	1.0	7.55	6.40
74			2	1.0	6.65	6.70
75			2	1.0	7.55	6.60
76			2	0.8	6.40	6.80
77			2	1.0	7.55	6.35
78			2	1.0	7.60	7.20
79			2	1.0	7.10	6.75
80			2	1.0	6.85	6.70
81			2	1.0	7.35	6.50
82			2	1.0	7.10	6.40
83			2	1.0	7.10	6.45
84			2	0.8	6.40	6.30
85			2	0.8	6.30	6.25
86			2	0.8	6.20	5.00
87			2	1.0	6.80	6.35
88			2	0.8	5.00	6.80
89			1	0.8	6.20	6.30
90			1	0.9	6.35	5.80
91			1	0.9	6.20	5.60
92			1	0.9	6.20	6.25
93			1	0.9	5.90	5.30
94[d]			2	0.8	6.15	6.85
95	c-Hex	H	2	1.0	6.80	6.00
96	c-Hex	H	3	1.0	6.40	6.30
97	c-Hex	Me	2	0.9	7.50	5.50
98	c-Hex	c-Hex	2	1.0	6.50	5.45

[a]ia (intrinsic activity) related to histamine = 1. pD_2 ± 0.1 (SEM), mean values of 3–6 independent experiments. [b]pK_B ± 0.2 (SEM), mean of 4–8 independent experiments. [c]Lit [1]: atrium: 48.1 x histamine, ileum: pA_2 = 5.47. [d]Lit [6]. [e]Lit [11] pD_2 = 7.7. [f]Lit [11] pA_2 = 6.3.

Table III. H_2 agonistic and H_1 antagonistic activity of α- and β-methyl-branched phenyl and cyclohexylalkylguanidines **99–106**.



Compd.	R^1	R^2	R^3	R^4	Atrium[a] i. a.	Atrium[a] pD_2 ± 0.1	Ileum[b] pK_B ± 0.2
99	Ph	H	H	Me	1.0	6.30	5.80
100	c-Hex	H	H	Me	1.0	6.30	6.50
101	c-Hex	c-Hex	H	Me	0.7	4.90	6.10
102	c-Hex	c-Hex	Me	H	0.9	6.40	6.25
103	Ph	Ph	H	Me	0.8	7.35	6.65
104	Ph	Ph	Me	H	1.0	7.40	6.30
105	4-FPh	4-FPh	H	Me	1.0	6.20	6.20
106	4-FPh	4-FPh	Me	H	1.0	7.20	6.40

[a,b]See footnotes to table II.

achieving about 50% of the maximal response. The higher potency of **65** *vs* **64** gives further evidence for the activity-enhancing effect of fluorine substitution as also found in the arpromidine series. The rank order of potency in the Langendorff heart arpromidine > **65** > impromidine > **64** > **56** is quite similar to that in the isolated guinea pig atrium. However, in the perfused heart the positive chronotropic response is significantly lower for arpromidine, **56** and **65** than for impromidine and **64**, indicating a more favourable inotropism/chronotropism ratio for the fluorinated diarylalkylguanidines and **56**. This tendency is more pronounced *in vivo* in guinea pigs, as demonstrated for some fluorinated apromidine analogues that were surprisingly found to be about 100 times more potent as inotropes than impromidine and tending to decrease heart rate under conditions revealing impromidine mainly as a positive chronotropic agent [44].

Conclusion

The pyridine ring in arpromidine may be replaced by phenyl resulting in H_2 agonists achieving maximally about half the potency of the chemical lead. However, the structure–activity relationships found in arpromidine-like compounds may not be completely transferred to the diphenylalkylguanidine series, *eg* concerning the optimal substitution pattern. As demonstrated by some cyclohexyl analogues, aromatic rings are not required at all in the affinity-conferring portion to produce relatively high H_2-agonist potency. However, phenyl rings may be useful for combined H_2 agonistic/H_1 antagonistic activity.

Experimental protocols

Chemical synthesis

Melting points (uncorrected) were determined on a Büchi apparatus. Elemental analyses, indicated by elemental symbols, were within ± 0.4% of the theoretical values and were performed at the analytical department of the Institute of Pharmacy, Freie Universität Berlin. The structures were confirmed by ^{1}H NMR (Bruker WP 60 (60 MHz) or Bruker WM 250 (250 MHz), TMS as internal standard) and by mass spectroscopy (EI: Finnigan MAT CH7A (170°C, 70 eV) or MAT 711 (200°C, 80 eV); FAB: Finnigan MAT CH5DF ($^+$FAB, xenon, DMSO/glycerol)). ^{1}H NMR data are given only exemplarily in *Experimental protocols* because of the structural resemblance of compounds synthetized according to general procedures. Chromatographic separations in a preparative scale were carried out on a Chromatotron 7924T (Harrison Research) using glass rotors with 4-mm layers of silica gel 60 PF_{254} containing gypsum (Merck). Short-path distillations were performed with a Kugelrohr apparatus (Büchi GKR 50).

*Benzoylguanidines **1–53***

A mixture of the respective primary amine base (5 mmol) and diphenyl benzoylcarbonimidate (5 mmol) was stirred in CH_2Cl_2 (20 ml) for 15 min at ambient temperature and subsequently evaporated. The residue was dissolved in pyridine (30 ml), 5.5 mmol of 3-(imidazol-4-yl)propanamine was added and the solution refluxed for 1–2 h (TLC control). After evaporation *in vacuo*, the remaining oil was dissolved in 5% HCl and

Table IV. Effects of guanidines **56**, **64** and **65** *versus* impromidine on isolated perfused guinea pig hearts.

Compound	*Δ LV dp/dt_{max}*[a]	*Relative potency*[b]	*Δ Heart rate*[a]	*Δ Coronary flow*[a]
Impromidine	100	100	100	100
Arpromidine[c]	97 ± 3.6	146	57 ± 8	143 ± 17.5
56	82 ± 3.9	30	59 ± 6.3	95 ± 16.9
64	52 ± 3.0	77	93 ± 6.4	165 ± 20.4
65	94 ± 2.7	132	47 ± 9.1	111 ± 6.8

[a]Mean ± SEM (n = 6) calculated from the net increase in LV dp/dt_{max}, heart rate, and coronary flow *versus* impromidine = 100% in the corresponding control group (n = 6). [b]Relative potency calculated from molar ED_{50} ratios, relative to impromidine = 100%. [c]Lit [6, 10].

extracted with Et_2O to remove phenol. The aqueous layer was basified with ammonia and extracted with CH_2Cl_2. The crude benzoylguanidines were purified chromatographically (Chromatotron; $CHCl_3$ – MeOH, 99:1 – 95:5, ammonia atmosphere) and recrystallized from MeCN or as indicated in table I. Yield 50–60%.

For analytical data of new compounds, see table I. The benzoylguanidines required as starting material for the preparation of guanidines **64**, **65**, **68**, **70**, **71**, **75**, **85**, **86**, **94** (see table II) have been described elsewhere [18, 6]. ^1H NMR ($CDCl_3$) of **14**: δ = 1.87 (m, 2H), 2.38 (q, *J* = 7 Hz, 2H), 2.64 (t, *J* = 6.5 Hz, 2H), 3.0–3.85 (br, 4H), 4.01 (t, *J* = 7.5 Hz, 1H), 6.73 (s, 1H), 6.9–7.5 (m, 12H), 8.12 (d, *J* = 7 Hz, 2H), 10.45 (br, 1H).

*Guanidines **54–106***

The benzoylguanidines **1–53** (1–2 mmol) were heated under reflux in 20% HCl (45 ml) for 5–10 h. After dilution with water benzoic acid was removed by extraction with Et_2O and the aqueous layer was evaporated to dryness *in vacuo*. The guanidines were obtained in 95–100% yield as chromatographically pure amorphous hygroscopic dihydrochlorides. For analytical purposes the compounds were converted into dipicrates by addition of a saturated aqueous solution of picric acid. Recrystallization from EtOH–H_2O.

For analytical data of new compounds, see table I. The guanidines **64**, **65**, **68**, **70**, **71**, **75**, **85**, **86**, **94** listed in table II have been described elsewhere [6, 18]. ^1H NMR (DMSO–d_6) of **67**·2HCl: δ = 1.83 (m, 2H), 2.26 (m, 2H), 2.71 (t, *J* = 7.5 Hz, 2H, Im-CH_2), 3.02 (m, 2H, CH_2NH), 3.17 (m, 2H, CH_2NH), 4.20 (t, *J* = 8 Hz, 1H), 7.2–7.55 (m, 11H; 9H ar, C=NH_2^+), 8.00 (br s, 2H, CH_2-N*H*), 9.05 (s, 1H, Im-2-H), 14.6 (br, 2H, imidazolium-NH).

*3-Cyclohexylpropanamine **109** and 5-phenylpentanamine **110***

A mixture of K-phthalimide (25 mmol) and the equimolar amount of 3-cyclohexylpropylchloride [19] or 5-phenylpentylchloride [20] in DMF (50 ml) was heated under reflux for 3 h. The chilled solution was poured onto 50 g of crushed ice and extracted with Et_2O. *N*-(3-Cyclohexylpropyl)phthalimide (**107**) and *N*-(5-phenylpentyl)phthalimide (**108**) crystallized from cold MeOH (5°C). **107**: Yield 85%, mp 51°C. MS: *m/z* (rel int, %) = 271 ($M^{+\cdot}$, 100). Anal $C_{17}H_{21}NO_2$ (C, H, N). **108**: Yield 85%, mp 35°C. Anal $C_{19}H_{19}NO_2$ (C, H, N).

Phthalimides **107** or **108** (20 mmol) and 1 ml of hydrazine hydrate were refluxed in EtOH (10 ml) for 20 min. Insoluble material was filtered off and washed with EtOH. The filtrate was evaporated affording the oily bases of amines **109** and **110** that were distilled *in vacuo* (**109**: Yield 94%, $bp_{1.2}$ = 60–62°C [21]. **110**: Yield 95%, bp_{10} = 135–136°C [22]) and characterized as picrates. **109** picrate: mp = 164°C (from EtOH), Anal $C_9H_{19}N{\cdot}C_6H_3N_3O_7$ (C, H, N). **110** picrate: mp 154°C (from EtOH), Anal $C_{11}H_{17}N{\cdot}C_6H_3N_3O_7$ (C, H, N).

*3,3-Disubstituted methyl 2-cyanopropanoates **116–135***

A mixture of methyl cyanoacetate (0.2 mol), the equimolar amount of the requisite halogenated benzaldehyde, β-alanine (4 mmol), acetic acid (40 mmol) and 50 ml of toluene was heated under reflux using a water trap. The methyl 2-cyano-3-(R^1)-2-propenoates **111–115** (mixtures of Z/E-isomers) precipitating on concentration of the solution were filtered off, triturated with water and recrystallized from toluene (**111–114**) or acetone (**115**). Yield: 90–95%. The following 3-substituted methyl 2-cyanopropenoates were obtained: 3-(3-Fluorophenyl)-~, **111**: mp = 101°C (Lit [23] mp = 103°C). 3-(3,4-Difluorophenyl)-~, **112**: mp = 107°C. Anal $C_{11}H_7F_2NO_2$ (C, H, N). 3-(4-Chlorophenyl)-~, **113**: mp = 125°C (Lit [24] mp = 125°C). 3-(3-Chlorophenyl)-~, **114** [25]: mp = 111°C. Anal $C_{11}H_8ClNO_2$ (C, H, N). 3-(3,4-Dichlorophenyl)-~, **115**: mp = 144°C (Lit [26] mp = 145°C).

A solution of Grignard reagent, freshly prepared from the respective bromobenzene (20 mmol) and 0.49 g of Mg in Et_2O (30 ml), was dropped with vigorous stirring into a solution of **111–115** (15 mmol) in 30 ml of absolute benzene. The mixture was refluxed for 1 h and subsequently poured onto crushed ice. The precipitate formed was dissolved by addition of 5% HCl, the organic layer separated, the aqueous solution extracted with Et_2O; the etheric solutions were combined, washed with aqueous $NaHCO_3$ and water and dried over Na_2SO_4. Evaporation yielded 60–70% of the 3,3-disubstituted methyl 2-cyanopropanoates **116–135** as oils that were directly employed for further reaction. Exemplarily, methyl 2-cyano-3,3-bis(3-fluorophenyl)propanoate **116** and methyl 2-cyano-3,3-bis(3-chlorophenyl)propanoate **117** were crystallized from EtOH. **116**: Yield 68%, mp = 78°C. MS: *m/z* (rel int, %) = 301 ($M^{+\cdot}$, 14), 203 (100). ^1H NMR (DMSO–d_6): δ = 3.62 (s, 3H), 4.86 (d, *J* = 10.5 Hz, 1H), 5.41 (d, *J* = 10.5 Hz, 1H), 7.05–7.15 (m, 2H), 7.25–7.45 (m, 6H). Anal $C_{17}H_{13}F_2NO_2$ (C, H, N). **117**: Yield 65%, mp = 94°C. MS: *m/z* (rel int, %) = 333 ($M^{+\cdot}$, 8), 235 (100). Anal $C_{17}H_{13}Cl_2NO_2$ (C, H, N).

*3,3-Disubstituted 2-carbamoylpropanoic acids **136–148***

The corresponding esters **116–135** (10 mmol) were refluxed for 15 min in a mixture of MeOH (5 ml) and 5% NaOH (10 ml). MeOH was removed *in vacuo* and the residue washed with ether, acidified with 5% HCl and extracted with Et_2O. After concentration of the organic layer the products crystallized from Et_2O–petroleum ether. Recrystallization from Et_2O or MeCN. The following 3,3-disubstituted 2-carbamoylpropanoic acids were obtained: 3-(3-Fluorophenyl)-3-phenyl-~, **136**: hygroscopic, MS: *m/z* (rel int, %) = 287 ($M^{+\cdot}$, 7), 243 (85), 185 (100). ^1H NMR (DMSO–d_6): δ = 4.40 (d, *J* = 12 Hz, 1H), 4.66 (d, *J* = 12 Hz, 1H), 7.05–7.55 (m, 9H), 12.5 (br, 1H, COOH). 3,3-Bis(3-fluorophenyl)-~, **137**: not isolated. 3-(3,4-Difluorophenyl)-3-phenyl-~, **138**: mp = 152°C (MeCN). Anal $C_{16}H_{13}F_2NO_3{\cdot}1/2H_2O$ (C, H, N). 3-(3,4-Difluorophenyl)-3-(4-fluorophenyl)-~, **139**: mp = 186°C (MeCN). Anal $C_{16}H_{12}F_3NO_3{\cdot}1/2H_2O$ (C, H, N). 3-(3,4-Dichlorophenyl)-3-(4-fluorophenyl)-~, **140**: mp = 136°C (Et_2O). Anal $C_{16}H_{12}Cl_2FNO_3$ (C, H, N). 3-(3,4-Difluorophenyl)-3-(3-fluorophenyl)-~, **141**: mp = 137°C (MeCN). Anal $C_{16}H_{12}F_3NO_3$ (C, H, N). 3-(4-Chlorophenyl)-3-(3-fluorophenyl)-~, **142**: mp = 143°C (MeCN). Anal $C_{16}H_{13}ClFNO_3$ (C, H, N). 3-(3-Chlorophenyl)-3-(3-fluorophenyl)-~, **143**: mp = 142°C (MeCN). Anal $C_{16}H_{13}ClFNO_3$ (C, H, N). 3,3-Bis(3,4-difluorophenyl)-~, **144**: mp = 136°C (MeCN). Anal $C_{16}H_{11}F_4NO_3$ (C, H, N). 3-(4-Chlorophenyl)-3-(3,4-difluorophenyl)-~, **145**: mp = 138°C (MeCN). Anal $C_{16}H_{12}ClF_2NO_3$ (C, H, N). 3-(3-Chlorophenyl)-3-(3,4-difluorophenyl)-~, **146**: mp = 140°C (MeCN). $C_{16}H_{12}ClF_2NO_3$ (C, H, N). 3,3-Bis(3-chlorophenyl)-~, **147**: mp = 144°C (Et_2O). Anal $C_{16}H_{13}Cl_2NO_3$ (C, H, N). 3-(3-Chlorophenyl)-3-(3,4-dichlorophenyl)-~, **148**: mp = 125°C (Et_2O). $C_{16}H_{12}Cl_3NO_3$ (C, H, N).

*3,3-Disubstituted 2-cyanopropanoic acids **149–155***

The respective methyl 2-cyanopropanoates **116–135** (10 mmol) were refluxed for 15 min in 10 ml of 5% aqueous NaOH. The mixture was washed with ether, acidified with 5% HCl and extracted with Et_2O. After evaporation of the organic layer the products crystallized from $CHCl_3$–Et_2O. Recrystallization from Et_2O or MeCN. The following 3,3-disubstituted 2-cyanopropanoic acids were obtained: 3-(3-Chlorophenyl)-3-phenyl-~, **149**: mp = 158°C (Et_2O). MS: *m/z* (rel int, %) = 285

($M^{+\cdot}$, 17), 241 (20), 201 (100). ^{1}H NMR (DMSO–d_6): δ = 4.38 (d, *J* = 12.5 Hz, 1H), 4.61 (d, *J* = 12.5 Hz, 1H), 7.01 (d, *J* = 10 Hz, 1H), 7.05–7.4 (m, 6H), 7.53 (d, *J* = 8.5 Hz, 1H), 12.55 (br, 1H, COOH). Anal $C_{16}H_{12}ClNO_2$ (C, H, N). 3-(3-Fluorophenyl)-3-(4-fluorophenyl)-~, **150**: mp = 151°C (Et_2O). Anal $C_{16}H_{11}F_2NO_2$ (C, H, N). 3-(4-Chlorophenyl)-3-(4-fluorophenyl)-~, **151**: mp = 168°C (Et_2O). Anal $C_{16}H_{11}ClFNO_2$ (C, H, N). 3-(3-Chlorophenyl)-3-(4-fluorophenyl)-~, **152**: mp = 156°C (MeCN). $C_{16}H_{11}ClFNO_2 \cdot H_2O$ (C, H, N). 3,3-Bis(4-chlorophenyl)-~, **153**: mp = 177°C (Et_2O). Anal $C_{16}H_{11}Cl_2NO_2$ (C, H, N). 3-(3-Chlorophenyl)-3-(4-chlorophenyl)-~, **154**: mp = 162°C (Et_2O). Anal $C_{16}H_{11}Cl_2NO_2$ (C, H, N). 3-(3,4-Dichlorophenyl)-3-(4-chlorophenyl)-~, **155**: mp = 162°C (Et_2O). Anal $C_{16}H_{10}Cl_3NO_2$ (C, H, N).

*3,3-Diphenylpropanamines **156–175***

Method A. Carboxamides **136–148** (8 mmol) in 20 ml of tetraline were heated for 15 min at 160–165°C (**139**: 180°C). The cold solution was dropped with stirring into a suspension of $LiAlH_4$ (8.8 mmol) in Et_2O (20 ml) and subsequently refluxed on a water bath for 60 min. The mixture was cooled with ice and 4 ml of water, 4 ml of 5% aqueous NaOH and 16 ml of water were consecutively added. The precipitate was removed by filtration, the organic layer separated and the solvent removed *in vacuo*. The residue was distilled (short-path distillation, bath temperature$_{0.5}$ 200–220°C) affording the amines as colorless or slightly yellow oils.

Method B. Nitriles **149–155** (8 mmol) in 20 ml tetraline were heated at 160–165°C (**151**, **152**: 175–180°C) for 30 min. Reduction and hydrolysis was carried out as described for *Method A* using 4.4 mmol of $LiAlH_4$ and 2 ml of water, 2 ml of 5% NaOH and 4 ml of water, respectively. The following 3,3-disubstituted propanamines were obtained in 75–85% yield and characterized as picrates or hydrochlorides.

Method A. 3-(3-Fluorophenyl)-3-phenylpropanamine, **156** [26]: mp (picrate) = 171°C (MeOH). MS: *m/z*(rel int, %) = 229 ($M^{+\cdot}$, 66), 212 (100), 186 (33), 185 (30). ^{1}H NMR (DMSO–d_6): δ = 2.30 (q, *J* = 8 Hz, 2H, $CHCH_2CH_2$), 2.69 (t, *J* = 8 Hz, 2H, CH_2N), 4.12 (t, *J* = 8 Hz, 1H, *CH*), 7.0–7.1 (m, 1H), 7.15 – 7.25 (m, 3H), 7.3–7.4 (m, 5H), 7.7 (br, 3H, NH_3^+). 8.62 (s, 2H, picrate). Anal $C_{15}H_{16}FN \cdot C_6H_3N_3O_7$ (C, H, N). 3-(3,4-Difluorophenyl)-3-phenyl-~, **157**: mp = 156°C (EtOH). Anal $C_{15}H_{15}F_2N \cdot C_6H_3N_3O_7$ (C, H, N). 3-(3,4-Difluorophenyl)-3-(4-fluorophenyl)-~, **158**: mp = 186 (MeOH – H_2O). Anal $C_{15}H_{14}F_3N \cdot C_6H_3N_3O_7$ (C, H, N). 3-(3,4-Dichlorophenyl)-3-(4-fluorophenyl)-~, **159**: mp = 186°C (EtOH). Anal $C_{15}H_{14}Cl_2FN \cdot C_6H_3N_3O_7$ (C, H, N). 3,3-Bis(3-fluorophenyl)-~, **160**: mp = 186°C (MeOH–H_2O). $C_{15}H_{15}F_2N \cdot C_6H_3N_3O_7$ (C, H, N). 3-(3,4-Difluorophenyl)-3-(3-fluorophenyl)-~, **161**: mp = 184°C (MeOH – H_2O). $C_{15}H_{14}F_3N \cdot C_6H_3N_3O_7$ (C, H, N). 3-(4-Chlorophenyl)-3-(3-fluorophenyl)-~, **162** [26]: mp = 184°C (MeOH – H_2O). $C_{15}H_{15}ClFN \cdot C_6H_3N_3O_7$ (C, H, N). 3-(3-Chlorophenyl)-3-(3-fluorophenyl)-~, **163**: mp = 171°C (MeOH – H_2O). Anal $C_{15}H_{15}ClFN \cdot C_6H_3N_3O_7$ (C, H, N). 3,3-Bis(3,4-difluorophenyl)-~, **164**: mp = 194°C (EtOH). Anal $C_{15}H_{13}F_4N \cdot C_6H_3N_3O_7$ (C, H, N). 3-(4-Chlorophenyl)-3-(3,4-difluorophenyl)-~, **165**: mp = 185°C (Et_2O). Anal $C_{15}H_{14}ClF_2N \cdot HCl$ (C, H, N). 3-(3-Chlorophenyl)-3-(3,4-difluorophenyl)-~, **166**: mp = 187°C (MeOH – H_2O). Anal $C_{15}H_{14}ClF_2N \cdot C_6H_3N_3O_7$ (C, H, N). 3,3-Bis(3-chlorophenyl)-~, **167**: mp = 193°C (Et_2O). $C_{15}H_{15}Cl_2N \cdot C_6H_3N_3O_7$ (C, H, N). 3-(3,4-Dichlorophenyl)-3-(3-chlorophenyl)-~, **168**: mp = 208°C (EtOH – H_2O). Anal $C_{15}H_{14}Cl_3N \cdot C_6H_3N_3O_7$ (C, H, N).

Method B. 3-(3-Chlorophenyl)-3-phenylpropanamine **169**: mp = 155°C (EtOH). Anal $C_{15}H_{16}ClN \cdot C_6H_3N_3O_7$ (C, H, N). 3-(3-Fluorophenyl)-3-(4-fluorophenyl)-~, **170**: mp = 165°C (MeOH – H_2O). Anal $C_{15}H_{15}F_2N \cdot C_6H_3N_3O_7$ (C, H, N). 3-(3-Chlorophenyl)-3-(3-fluorophenyl)-~, **171**: mp = 181°C (EtOH – H_2O). Anal $C_{15}H_{15}ClFN \cdot C_6H_3N_3O_7$ (C, H, N). 3-(3-Chlorophenyl)-3-(4-fluorophenyl)-~, **172**: mp = 183°C (EtOH – H_2O). Anal $C_{15}H_{15}ClFN \cdot C_6H_3N_3O_7$ (C, H, N). 3,3-Bis(4-chlorophenyl)-~, **173** [26]: mp = 222°C (Et_2O). Anal $C_{15}H_{15}Cl_2N \cdot HCl$ (C, H, N). 3-(3-Chlorophenyl)-3-(4-chlorophenyl)-~, **174** [26]: mp = 169°C (Et_2O). Anal $C_{15}H_{15}Cl_2N \cdot HCl$ (C, H, N). 3-(3,4-Dichlorophenyl)-3-(4-chlorophenyl)-~, **175** [26]: mp = 208°C (EtOH – H_2O). Anal $C_{15}H_{14}Cl_3N \cdot C_6H_3N_3O_7$ (C, H, N).

*2,3-Diphenylpropanenitriles **176–180***

The requisite benzylcyanides (50 mmol) were added over a 1-h period to a suspension of sodium (50 mmol) in anhydrous Et_2O under N_2. The mixture was refluxed for 60–90 min to complete the formation of the sodium salt. The appropriate benzylchlorides (25 mmol), dissolved in Et_2O (20 ml), were dropped into the chilled mixture and subsequently heated under reflux for 2 h. To the cold mixture 20 ml of 1.2 M–HCl was added slowly and the product isolated by extraction with Et_2O. The organic layer was washed with a solution of $NaHCO_3$ and water, dried over Na_2SO_4 and evaporated *in vacuo*. The products were purified by short-path distillation *in vacuo* (bath temperature$_{0.4-1.0}$ 200–230°C).

The following 2,3-disubstituted propanenitriles were obtained in 60–70% yield: 2,3-Bis(4-fluorophenyl)propanenitrile **176**: mp = 96°C (EtOAc). MS: *m/z* (rel int, %) = 243 ($M^{+\cdot}$, 36), 109 (100). ^{1}H NMR (DMSO–d_6): δ = 3.17 (d, *J* = 8 Hz, 2H), 4.58 (t, *J* = 8 Hz, 1H), 7.1–7.3 (m, 6H), 7.4–7.45 (m, 2H). Anal $C_{15}H_{11}F_2N$ (C, H, N). 2-(4-Fluorophenyl)-3-(3-fluorophenyl)-~, **177**: mp = 57°C (petroleum ether – Et_2O). Anal $C_{15}H_{11}F_2N$ (C, H, N). 3-(4-Chlorophenyl)-2-(4-fluorophenyl)-~, **178**: mp = 90°C (petroleum ether – Et_2O). Anal $C_{15}H_{11}ClFN$ (C, H, N). 2-(4-Chlorophenyl)-3-(4-fluorophenyl)-~, **179**: mp = 99°C (petroleum ether – Et_2O) (Lit [27] mp = 100°C). 2,3-Bis(4-chlorophenyl)-~, **180**: $Bp_{0.4}$ = 225°C bath temp (Lit [28] mp = 90–92.5°C).

*Alkenenitriles **183–189***

Method A. Benzophenone or 4,4'-difluorobenzophenone (50 mmol) in 70 ml of toluene were dropped with stirring to a mixture of propanenitrile (55 mmol) and $NaNH_2$ (50 mmol) in 30 ml of anhydrous toluene. The solution was refluxed for 2 h and subsequently poured onto crushed ice. The hydroxynitriles were isolated by extraction with Et_2O and were recrystallized from toluene. 3-Hydroxy-2-methyl-3,3-diphenylpropanenitrile **181**: Yield 55%, mp = 123°C (Lit [29] mp = 125°C). 3-Hydroxy-2-methyl-3,3-bis(4-fluorophenyl)propanenitrile **182**: Yield 51%, mp = 133°C. Anal $C_{16}H_{13}F_2NO$ (C, H, N). Hydroxynitriles **181**, **182** (20 mmol) were refluxed with 98% formic acid (150 ml) for 30 min and subsequently poured into 150 ml of ice-water. The products were extracted with cyclohexane and crystallized from *n*-hexane. 2-Methyl-3,3-diphenylpropenenitrile **183**: Yield 90%, mp = 63°C (Lit [29] mp = 59–61°C). 3,3-Bis(4-fluorophenyl)-2-methylpropenenitrile **184**: Yield 91%, mp = 75°C. Anal $C_{16}H_{11}F_2N$ (C, H, N).

Method B. Diethyl cyanomethanephosphonate (7.2 ml) was added to NaOEt (40 mmol) in EtOH (40 ml). Subsequently, a solution of 40 mmol of the respective ketone in EtOH (20 ml) was added dropwise and stirred for 5 h at ambient temperature. The solvent was removed *in vacuo*, water (50 ml) was added and the alkenenitriles were isolated by extraction with Et_2O and purified by short-path distillation *in vacuo*. The following alkenenitriles were obtained in 72–78% yield as mixtures of Z/E-isomers, that were directly employed for further reaction: 3-Phenyl-2-butenenitrile **185**: $bp_{0.05}$ = 120°C bath temp (Lit

[30] bp_4 = 111–131). MS: *m/z* (rel int, %) = 157 ($M^{+\cdot}$, 100). 3-Phenyl-2-pentenenitrile **186**: bp_1 = 190°C bath temp (Lit [31] bp_{13} = 147°C). MS: *m/z* (rel int, %) = 157 ($M^{+\cdot}$, 100). 3-(4-Fluorophenyl)-2-butenenitrile **187** [32]: $bp_{0.8}$ = 130°C bath temp mp = 53°C (hexane – EtOAc). MS: *m/z* (rel int, %) = 161 ($M^{+\cdot}$, 100). 3-(4-Fluorophenyl)-2-pentenenitrile **188**: $bp_{0.8}$ = 170°C bath temp MS: *m/z* (rel int, %) = 175 ($M^{+\cdot}$, 100). 3,3-Bis(4-fluorophenyl)propenenitrile **189**: mp = 80°C (*c*-hexane) (Lit [33] mp = 79–81°C).

*Alkenamines **190–196***

Alkenenitriles **183–189** were treated with $LiAlH_4$ and isolated as described below for the amines **197–201** affording 75–85% yield of the following alkenamines as mixtures of Z/E isomers that were directly employed as hydrochlorides for the synthesis of amines **202–208**: 2-Methyl-3,3-diphenyl-2-propen-1-amine **190**: mp (picrate) = 174°C (EtOH – H_2O) (Lit [29] **190**: HCl: mp = 233–235°C). MS: *m/z* (rel int, %) = 223 ($M^{+\cdot}$, 63), 208 (100). Anal $C_{16}H_{17}N{\cdot}C_6H_3N_3O_7$ (C, H, N). 3,3-Bis(4-fluorophenyl)-2-methyl-2-propen-1-amine **191**: mp = 245°C (EtOH – Et_2O). Anal $C_{16}H_{15}F_2N{\cdot}HCl$ (C, H, N). 3-Phenyl-2-buten-1-amine **192**: mp = 214°C (Me_2CO – Et_2O). $C_{10}H_{13}N{\cdot}HCl$ (C, H, N). 3-Phenyl-2-penten-1-amine **193**: mp = 178–179°C (Me_2CO). Anal $C_{11}H_{15}N{\cdot}HCl$. 3-(4-Fluorophenyl)-2-buten-1-amine **194**: mp = 209°C (Me_2CO). Anal $C_{10}H_{12}FN{\cdot}HCl$ (C, H, N). 3-(4-Fluorophenyl)-2-penten-1-amine **195**: mp = 193°C (Et_2O). $C_{11}H_{14}FN{\cdot}HCl$ (C, H, N). 3,3-Bis(4-fluorophenyl)-2-propen-1-amine **196**: MS: *m/z* (rel int, %) = 245 ($M^{+\cdot}$, 25), 230 (95), 203 (100).

*2,3-Diphenylpropanamines **197–201***

Nitriles **176–180** (20 mmol) were dissolved in Et_2O (20 mmol), added to a suspension of $LiAlH_4$ (11 mmol) in anhydrous Et_2O (30 ml) and refluxed for 30 min. The mixture was hydrolysed by slow consecutive addition of 4 ml of water, 4 ml of 5% NaOH and 16 ml of water. Insoluble material was filtered off, the organic layer was separated, dried over Na_2SO_4 and evaporated. The remaining oil was purified by short-path distillation *in vacuo*.

The following amines were obtained in 80–90% yield and characterized as hydrochlorides or picrates: 2,3-Bis(4-fluorophenyl)propanamine **197**: mp (hydrochloride) = 155°C (EtOH). MS: *m/z* (rel int, %) = 247 ($M^{+\cdot}$, 27), 109 (100). ^1H NMR (DMSO–d_6): δ = 2.78 (m, 1H), 3.05–3.15 (m, 3H), 3.26 (m, 1H), 7.0–7.15 (m, 6H), 7.25–7.35 (m, 2H). 8.15 (br s, 3H, NH_3^+). Anal $C_{15}H_{15}F_2N{\cdot}HCl$ (C, H, N). 2-(4-Fluorophenyl)-3-(3-fluorophenyl)propanamine, **198**: $bp_{0.05}$ = 170–190°C bath temp; mp (picrate) = 206°C (MeOH). Anal $C_{15}H_{15}F_2N{\cdot}C_6H_3N_3O_7$ (C, H, N). 3-(4-Chlorophenyl)-2-(4-fluorophenyl)-propanamine **199**: $bp_{0.05}$ = 175°C bath temp; mp (hydrochloride) = 211°C (MeOH). Anal $C_{15}H_{15}ClFN{\cdot}HCl$. 2-(4-Chlorophenyl)-3-(4-fluorophenyl)propanamine **200**: $bp_{0.1}$ = 160°C bath temp (Lit [27] bp_6 = 176–178°C); mp (picrate) = 176°C (MeOH – H_2O). Anal $C_{15}H_{15}ClFN{\cdot}C_6H_3N_3O_7$ (C, H, N). 2,3-Bis(4-chlorophenyl)propanamine **201**: mp (hydrochloride) = 176°C (H_2O) (base, Lit [27] bp_6 = 188–190°C). Anal $C_{15}H_{15}Cl_2N{\cdot}HCl$ (C, H, N).

*Primary amines **202–208***

Alkenamines **190–196**·HCl (5.5 mmol) were hydrogenated over 10% Pd-C catalyst (200 mg) at 8 bar in EtOH (50 ml) (**190**: 48 h; **191–196**: 24 h). The catalyst was filtered off, and the crude alkanamine hydrochlorides were quantitatively crystallized by addition of Et_2O.

The following amines were obtained and characterized as hydrochlorides or picrates: 2-Methyl-3,3-diphenylpropanamine **202**: mp (picrate) = 180°C (Lit [29] **202**·HCl: mp = 248–250°C). MS: *m/z* (rel int, %) = 225 ($M^{+\cdot}$, 72) 208 (100). ^1H NMR (CD_3OD) of **202**·HCl: δ = 0.98 (d, *J* = 6.5 Hz, 3H), 2.64–2.88 (m, 3H), 3.67 (d, *J* = 11 Hz, 1H), 7.15–7.2 (m, 2H), 7.25–7.4 (m, 8H). Anal $C_{16}H_{19}N{\cdot}C_6H_3N_3O_7{\cdot}1/2H_2O$ (C, H, N). 3,3-Bis(4-fluorophenyl)-2-methylpropanamine **203**: mp = 248°C (Me_2CO). Anal $C_{16}H_{17}F_2N{\cdot}HCl$ (C, H, N). 3-Phenylbutanamine **204**: Picrate, mp = 136°C (EtOH – H_2O) (Lit [34] base, bp_{11} = 98°C). Anal $C_{10}H_{15}N{\cdot}C_6H_3N_3O_7$ (C, H, N). 3-Phenylpentanamine **205**: mp (hydrochloride) = 120°C (Et_2O) (Lit [35] mp = 125–127°C). 3-(4-Fluorophenyl)butanamine **206**: $bp_{0.1}$ = 120°C bath temp; mp (hydrochloride) = 151°C (Et_2O). Anal $C_{10}H_{14}FN{\cdot}HCl$ (C, H, N). 3-(4-Fluorophenyl)-pentanamine **207**: mp = 140°C (Me_2CO). Anal $C_{11}H_{16}FN{\cdot}HCl$ (C, H, N). 3,3-Bis(4-fluorophenyl)propanamine **208**: mp = 137°C (Lit [33] mp (hydrochloride) = 138–139°C).

*4,4-Bis(4-fluorophenyl)-2-butanone **210***

Ethyl acetoacetate (50 mmol) was dropped with stirring into a suspension of sodium (1.15 g) in anhydrous THF (50 ml). Bis(fluorophenyl)methylchloride (55 mmol) was added dropwise and the mixture stirred for 8 h. The solvent was removed *in vacuo* and the residue dissolved in ice-cold water. Ethyl 2,2-[bis(4-fluorophenyl)methyl]-3-oxopentanoate **209** was extracted with Et_2O, distilled *in vacuo* (bp_3 = 120–130°C) and crystallized from MeOH. Yield 85%, mp = 83°C. MS: *m/z* (rel int, %) = 332 ($M^{+\cdot}$, < 1), 314 (100). Anal $C_{19}H_{18}F_2O_3$ (C, H).

The β-ketoester **209** (40 mmol) was treated with 5% aqueous NaOH (60 ml) at ambient temperature for 1 h and subsequently refluxed for 2 h. Ketone **210** was extracted with Et_2O, distilled *in vacuo* (short-path distillation, $bp_{0.4}$ = 220°C bath temp), and crystallized from cyclohexane–petroleum ether. Yield 70%, mp = 49°C. MS: *m/z* (rel int, %), = 260 ($M^{+\cdot}$, 23), 203 (100). ^1H NMR ($CDCl_3$): δ = 2.09 (s, 3H), 3.13 (d, *J* = 7.5 Hz, 2H), 4.57 (t, *J* = 7.5 Hz, 1H), 6.9–7.05 (m, 4H), 7.1–7.2 (m, 4H). Anal $C_{16}H_{14}F_2O$ (C, H).

*4,4-Diphenyl-2-butanamines **211**, **212** [36, 37]*

4,4-Diphenyl-2-butanone [38] or **210** (50 mmol) and ammonium formate (0.2 mol) were heated at 180°C using a water trap. The mixture was chilled and triturated with water. The insoluble residue was refluxed for 60 min with conc HCl. After dilution with water, the aqueous solution was basified with NaOH, the amines were extracted with Et_2O and subsequently purified by short-path distillation *in vacuo* as above. **211**: Yield 60%, mp (hydrochloride) = 168°C (Lit [36] mp = 175°C). **212**: Yield 53%, mp (picrate) = 205°C (EtOH), Anal $C_{16}H_{17}F_2N{\cdot}C_6H_3N_3O_7$ (C, H, N).

*Cyclohexyl- and dicyclohexylalkanamines **213–218***

The respective phenyl- or diphenylalkanamine hydrochlorides (10 mmol) were dissolved in EtOH (50 ml) and hydrogenated for 20 h at 50 bar over 300 mg of 5% Rh-C catalyst. The catalyst was removed by filtration, the solvent was evaporated affording the hydrochlorides of the following amines in quantitative yield: 4-Cyclohexyl-2-butanamine **213**: mp = 134°C (Et_2O). MS: *m/z* (rel int, %) = 155 ($M^{+\cdot}$, < 1), 44 (100). ^1H NMR (DMSO–d_6): δ = 0.87 (m, 2H), 0.95–1.3 (m, 6H), 1.19 (d, *J* = 6 Hz, 3H), 1.41 (m, 1H), 1.65 (m, 6H), 3.06 (m, 1H, C*H*-N), 8.17 (br, 3H, NH_3^+). Anal $C_{10}H_{21}N{\cdot}HCl$ (C, H, N). 3-Cyclohexyl-1-butanamine **214**: mp = 130°C (Et_2O). Anal $C_{10}H_{21}N{\cdot}HCl$ (C, H, N). 4-Cyclohexyl-1-butanamine **215**: mp = 165°C (Et_2O) (Lit [21] base bp_1 = 73°C). Anal $C_{10}H_{21}N{\cdot}HCl$ (C, H, N). 3,3-Dicyclohexyl-1-propanamine **216** [39]: mp = 171°C (Et_2O). Anal $C_{15}H_{29}N{\cdot}HCl$ (C, H, N). 4,4-Dicyclohexyl-2-butanamine **217**: mp = 188°C (Et_2O). Anal $C_{16}H_{31}N{\cdot}HCl$ (C, H, N). 3,3-Dicyclohexyl-2-methyl-1-propanamine **218**: mp = 201°C (Me_2CO). Anal $C_{16}H_{31}N{\cdot}HCl$ (C, H, N).

Pharmacological evaluation

H_2 agonism on the isolated spontaneously beating guinea pig right atrium [40]

Male guinea pigs (350–500 g) were sacrificed by a blow to 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 [40] and aerated with carbogen. The pD_2 values and intrinsic activites were determined from isometrically recorded cumulative concentration–response curves [41] as described [42] using histamine as the reference agonist (0.1–10 μM). Agonists were used as dihydrochlorides. The maximum effect of the agonist under study was completely abolished by 10–30 μM of cimetidine. H_2 receptor selectivity was verified by experiments in the presence of 1 μM of 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 in [42], using 20-ml organ baths containing Tyrode solution aerated with carbogen at 37°C. The guanidines were tested as hydrohalides at concentrations of 0.3–30 μM *versus* histamine after 10 min of incubation. Apparent pK_B ($-\log K_B$) values were calculated from the rightward shift of the histamine curve in the presence and absence of antagonist [41].

Contractility measurements on isolated perfused guinea pig hearts

Female guinea pigs weighing 300–450 g were sacrificed by a blow to the head. The hearts were rapidly excised and perfused according to the Langendorff technique with a modified Henseleit solution oxygenated with carbogen as described [43, 44]. The substances to be tested were injected as a bolus (15 μl) directly into the perfusion stream about 3 cm above the orifice of the coronary arteries. Coronary perfusion pressure as well as intraventricular pressure of the left and right ventricle were monitored as described in [44].

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References

1 Durant GJ, Duncan WAM, Ganellin CR, Parsons ME, Blakemore RC, Rasmussen AC (1978) *Nature (Lond)* 276, 403–405
2 Durant GJ, Ganellin CR, Hills DW, Miles PD, Parsons ME, Pepper ES (1985) *J Med Chem* 28, 1414–1422
3 Baumann G, Permanetter B, Wirtzfeld A (1984) *Pharmacol Ther* 24, 165–177
4 Buschauer A, Baumann G (1991) *Agents Actions* 33 suppl, 231–256
5 Van der Goot H, Bast A, Timmerman H (1991) *In: Histamine and Histamine Antagonists* (Uvnäs B, ed) *Handbook of Experimental Pharmacology*. Springer, Berlin, vol 97, 573–748
6 Buschauer A (1989) *J Med Chem* 32, 1963–1970
7 Buschauer A, Schickaneder H, Schunack W, Elz S, Szelenyi I, Baumann G, Ahrens KH (1986) EP 0199845; *Chem Abstr* 106, 84609y (1987)
8 Felix SB, Buschauer A, Baumann G (1991) *Agents Actions* 33 suppl, 257–269
9 Mörsdorf P, Engler H, Schickaneder H, Buschauer A, Schunack W, Baumann G (1990) *Drugs Fut* 15, 919–933
10 Baumann G, Buschauer A, Permanetter B, Schunack W (1988) *Inn Med* 15 suppl, 30–38
11 Sterk GJ, Koper J, van der Goot H, Timmerman H (1987) *Eur J Med Chem* 22, 491–498
12 Buschauer A (1987) *Arch Pharm (Weinheim)* 320, 377–378
13 Elz S, Schunack W (1987) *Z Naturforsch* 42B, 238–242
14 Buschauer A, Lachenmayr F, Schunack W (1991) *Pharmazie* 46, 840–845
15 Gantz I, Schäffer M, Del Valle J, Logsdon C, Campbell V, Uhler M, Yamada T (1991) *Proc Natl Acad Sci USA* 88, 429–433
16 Buschauer A (1988) *Arch Pharm (Weinheim)* 321, 415–418
17 Elz S, Schunack W (1988) *Arzneim-Forsch/Drug Res* 38, 327–332
18 Meindl W, Friese-Kimmel A, Lachenmayr F, Buschauer A, Schunack W (1990) *Arch Pharm (Weinheim)* 323, 267–272
19 Rossander S, Marvel C (1928) *J Am Chem Soc* 50, 1491–1496
20 Conant J, Kirner W (1924) *J Am Chem Soc* 46, 232–252
21 Skinner C, Gardner P, Shive W (1957) *J Am Chem Soc* 79, 2843–2846
22 Skinner C, Shive W, Ham R, Fitzgerald D, Eakin R (1956) *J Am Chem Soc* 78, 5097–5100
23 Lange J, Rump S, Galecka E (1977) *Pharmazie* 32, 82–84
24 Da Rocha Pitta I, Luu Duc C, Boucherle A, Pillon D (1974) *Eur J Med Chem* 9, 347–349
25 Silver R, Kerr K, Frandsen P, Kelly S, Holmes H (1967) *Can J Chem* 45, 1001–1006
26 Leditschke H, Rolly H, Schmidt-Ruppin H (1958) US 2 843 594; *Chem Abstr* 53, 16162f (1958)
27 Schorr M, Leditschke H, Fussgänger R, Bauer F (1961) DOS 1103936; *Chem Abstr* 56, 3409g (1962)
28 Jack D, Spickett R, Ganellin CR (1964) GB 959704; *Chem Abstr* 61, 4290b (1964)
29 Blank B, Zuccarello W, Cohen S, Frischmuth G, Scaricaciottoli D (1969) *J Med Chem* 12, 271–276
30 Vinograd L, Vulfson N (1959) *Zhur Obschei Khim* 29, 1147–1149; *Chem Abstr* 54, 1394e (1960)
31 Charles G (1963) *Bull Soc Chim Fr* 1559–1565
32 Boyle F (1984) EP 122693; *Chem Abstr* 102, 149273y (1985)
33 Ibanez-Paniello A (1973) *An Quim* 69, 1035–1045; *Chem Abstr* 80, 120422n (1974)
34 Fort A, Leary R (1960) *J Am Chem Soc* 82, 2494–2498
35 Testa E, Fontanella L, Aresi V (1964) *Liebigs Ann Chem* 673, 60–70
36 Yutaka K, Kyo F (1958) *Yakugaku Zasshi* 78, 551–553; *Chem Abstr* 52, 17196d (1958)
37 Zenno H, Saito Y, Nakaguchi O (1975) Jpn Kokai 7582043; *Chem Abstr* 83, 205923p (1975)
38 Burckhalter J, Johnson S (1951) *J Am Chem Soc* 73, 4830–4832
39 Atwal K, Reilly B, Ruby E, Turk C, Aberg G, Bergey J, Moreland S, Powell J (1987) *J Med Chem* 30, 627–635
40 Black JW, Duncan WAM, Durant GJ, Ganellin CR, Parsons ME (1972) *Nature (Lond)* 236, 385–390
41 Van Rossum JM (1963) *Arch Int Pharmacodyn Ther* 143, 299–330
42 Lennartz HG, Hepp M, Schunack W (1978) *Eur J Med Chem* 13, 229–234
43 Schrader J, Baumann G, Gerlach E (1977) *Pflügers Arch* 372, 29–35
44 Baumann G, Felix SB, Heidecke CD, Rieß G, Loher U, Ludwig L, Blömer H (1984) *Agents Actions* 15, 216–228