Synthesis and in Vitro Pharmacology of Arpromidine and Related Phenyl(pyridylalkyl)guanidines, a Potential New Class of Positive Inotropic Drugs[1]

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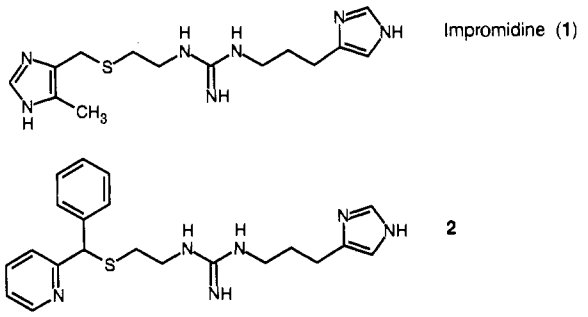
Replacement of the cimetidine moiety in impromidine (1, N^1-[3-(1*H*-imidazol-4-yl)propyl]-N^2-[2-[[(5-methyl-1*H*-imidazol-4-yl)methyl]thio]ethyl]guanidine) by more lipophilic H_2-nonspecific pheniramine-like structures resulted in potent H_2 agonists with up to 160 times the activity of histamine in the isolated, spontaneously beating guinea pig right atrium. Additionally, the compounds proved to be moderate H_1 antagonists. Highest H_2-agonistic potency was found in compounds characterized by a three-membered carbon chain connecting the aromatic rings and the guanidine group. The activity in the atrium was increased 2–4-fold by halogen substituents in the meta or para position of the phenyl ring. Highest H_1-antagonistic potency resides in the group of para-halogenated compounds, *p*-F representing the optimal substituent in both receptor models. The corresponding guanidine **52** (arpromidine, N^1-[3-(4-fluorophenyl)-3-pyridin-2-ylpropyl]-N^2-[3-(1*H*-imidazol-4-yl)propyl]guanidine) combines about 100 times the activity of histamine at the H_2 receptor with H_1-antagonistic potency in the range of pheniramine. Further increase in the activity on the atrium was achieved by disubstitution with halogen on the phenyl ring, such as 3,4-F_2, 3,5-F_2, and 3,4-Cl_2 (**63–65**). The 2-pyridyl group in arpromidine was replaced by 3-pyridyl without significant change in H_2 agonistic activity, whereas the 4-pyridyl and phenyl analogues were less active. The rank order of potency in the atrium was in good agreement with the positive inotropic effects found in isolated, perfused guinea pig hearts, where **63–65** were the most potent compounds as well.

At present, the development of new positive inotropic drugs[2] is dominated by the search for cardiotonics acting via alternative ways than myocardial membrane receptor stimulation, for example, by inhibition of the phosphodiesterase[3] or by increasing the calcium sensitivity of the contractile proteins.[4] Only very little attention is paid to the myocardial histamine H_2 receptor though Baumann et al.[5] have shown by using the selective H_2-agonist impromidine[6] in patients the stimulation of cardiac H_2 receptors to be an alternative promising approach in the treatment of catecholamine-insensitive congestive heart failure. In analogy to β-sympathomimetics, the positive inotropic effect of H_2 agonists is mediated by cAMP, but the histamine H_2-receptor adenylate cyclase system is not affected by the down-regulation of β-receptors owing to elevated endogenous catecholamine levels found in patients suffering from various heart diseases. Moreover, H_2 agonists do not only increase contractile force but show a beneficial dual mode of action by additionally lowering peripheral vascular resistance. The importance of vasodilator therapy is rapidly growing since the discovery of the ACE inhibitors, which have been demonstrated to produce short- and long-term clinical improvement in chronic heart failure and to decrease mortality.[7] As vasodilation is frequently associated with hypotension and renal insufficiency, if cardiac output does not adequately increase, additional positive inotropic stimulation may be required to improve cardiac performance.

Scheme I



Impromidine is not available as a drug. For general therapeutic application, substances are required with more beneficial properties than those of impromidine (**1**, Scheme I), e.g., less pronounced induction of rhythm disturbances, lower positive chronotropic effect, and more favorable heart/stomach activity ratio as well as activity after oral dosage. The present paper is part of an extensive research program for the development of such substances. In the beginning, **1** was considered the model compound. Impromidine is characterized by an (imidazolylpropyl)-guanidine moiety, which seems to be essential for the H_2-agonistic effect, and a structural part derived from the H_2-antagonist cimetidine, which is thought to confer high receptor affinity.[8,9] The structure was mainly modified in two ways: The "cimetidine-like" part was replaced by alternative groups which are known from antagonist series to contribute H_2-receptor affinity, such as imidazoles or thiazoles,[10] and by more lipophilic H_2-nonspecific structural parts, e.g., diaryl structures. Whereas the first variation revealed predominantly compounds with an impromidine-like profile of action, the latter modification resulted in H_2 agonists with interesting additional properties. Guanidine **2**[11] was found to be about 4 times more active

(1) Presented in part at the Jahrestagung der Deutschen Pharmazeutischen Gesellschaft, Münster, FRG, September 1987; Abstract A 22, (*Arch. Pharm. (Weinheim, Ger.)* **1987**, *320*, 888.), and the Xth International Symposium on Medicinal Chemistry, Budapest, Hungary, August 1988; Abstract P-27.
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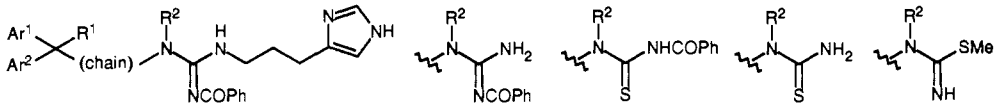
Table I. Structures and Formulas of Intermediates 3–32, 33–36, 37–40, and 41–45



3-31 32 33-36 37-40 41-45

compd no.	Ar^1	Ar^2	R^1	R^2	chain	% yield	mp,[a] °C	formula[b]
3	Ph	2-pyridyl	H	H	$(CH_2)_3$	50	135	$C_{29}H_{32}N_6O$
4	4-FC_6H_4	2-pyridyl	H	H	$(CH_2)_3$	58	141–142	$C_{29}H_{31}FN_6O$
5	Ph	2-pyridyl	H	H	$(CH_2)_2$	56	(56)	$C_{28}H_{30}N_6O$
6	4-MeC_6H_4	2-pyridyl	H	H	$(CH_2)_2$	54	(65)	$C_{29}H_{32}N_6O$
7	4-$MeOC_6H_4$	2-pyridyl	H	H	$(CH_2)_2$	48	(62)	$C_{29}H_{32}N_6O_2$
8	4-FC_6H_4	2-pyridyl	H	H	$(CH_2)_2$	58	(65)	$C_{28}H_{29}FN_6O$
9	4-ClC_6H_4	2-pyridyl	H	H	$(CH_2)_2$	56	(65)	$C_{28}H_{29}ClN_6O$
10	4-BrC_6H_4	2-pyridyl	H	H	$(CH_2)_2$	48	(69)	$C_{28}H_{29}BrN_6O$
11	4-$CF_3C_6H_4$	2-pyridyl	H	H	$(CH_2)_2$	41	(62)	$(C_{29}H_{29}F_3N_6O)$[c]
12	3-FC_6H_4	2-pyridyl	H	H	$(CH_2)_2$	49	(53)	$C_{28}H_{29}FN_6O$
13	3-ClC_6H_4	2-pyridyl	H	H	$(CH_2)_2$	58	(62)	$C_{28}H_{29}ClN_6O \cdot {}^1/_4H_2O$
14	3-$CF_3C_6H_4$	2-pyridyl	H	H	$(CH_2)_2$	56	(64)	$C_{29}H_{29}F_3N_6O \cdot {}^1/_2H_2O$
15	2-FC_6H_4	2-pyridyl	H	H	$(CH_2)_2$	51	(70)	$C_{28}H_{29}FN_6O$
16	2-ClC_6H_4	2-pyridyl	H	H	$(CH_2)_2$	44	(68)	$C_{28}H_{29}ClN_6O$
17	3,4-$F_2C_6H_3$	2-pyridyl	H	H	$(CH_2)_2$	48	(64)	$C_{28}H_{28}F_2N_6O$
18	3,5-$F_2C_6H_3$	2-pyridyl	H	H	$(CH_2)_2$	52	(65)	$C_{28}H_{28}F_2N_6O$
19	3,4-$Cl_2C_6H_3$	2-pyridyl	H	H	$(CH_2)_2$	50	(75)	$C_{28}H_{28}Cl_2N_6O$
20	3,5-$Cl_2C_6H_3$	2-pyridyl	H	H	$(CH_2)_2$	47	(67)	$C_{28}H_{28}Cl_2N_6O$
21	2,4-$Cl_2C_6H_3$	2-pyridyl	H	H	$(CH_2)_2$	41	(78)	$C_{28}H_{28}Cl_2N_6O$
22	4-FC_6H_4	2-pyridyl	H	Me	$(CH_2)_2$	57	(70)	$C_{29}H_{31}FN_6O \cdot {}^1/_2H_2O$
23	2-pyridyl	2-pyridyl	H	H	$(CH_2)_2$	38	116–117	$C_{27}H_{29}N_7O$
24[d]	4-FC_6H_4	2-pyridyl		H	$=CHCH_2$	40	(88)	$(C_{28}H_{27}FN_6O)$[e]
25	Ph	2-pyridyl	H	H	CH_2	39	145	$C_{27}H_{28}N_6O$
26	4-FC_6H_4	3-pyridyl	H	H	$(CH_2)_2$	47	(74)	$C_{28}H_{29}FN_6O \cdot {}^1/_4H_2O$
27	4-FC_6H_4	4-pyridyl	H	H	$(CH_2)_2$	51	(57)	$C_{28}H_{29}FN_6O \cdot {}^1/_4H_2O$
28	4-FC_6H_4	Ph	H	H	$(CH_2)_2$	52	128–130	$C_{29}H_{30}FN_5O \cdot {}^1/_4H_2O$
29	4-ClC_6H_4	Ph	H	H	$(CH_2)_2$	38	(66)	$C_{29}H_{30}ClN_5O$
30	3,4-$Cl_2C_6H_3$	Ph	H	H	$(CH_2)_2$	45	(73)	$C_{29}H_{29}Cl_2N_5O \cdot {}^1/_4H_2O$
31	4-FC_6H_4	benzyl	H	H	$(CH_2)_2$	53	(60)	$C_{30}H_{32}FN_5O$
32	4-FC_6H_4	2-pyridyl	H	H	$(CH_2)_2$	80	(58)	$C_{22}H_{21}FN_4O$
33	4-FC_6H_4	2-pyridyl	H	H	$(CH_2)_2$	91	90	$C_{22}H_{20}FN_3OS$
34	4-FC_6H_4	2-pyridyl	OH	H	$(CH_2)_2$	88	138–139	$C_{22}H_{20}FN_3O_2S$
35[d]	4-FC_6H_4	2-pyridyl		H	$=CHCH_2$	80	130	$C_{22}H_{18}FN_3OS$
36	2-thienyl	2-pyridyl	H	H	$(CH_2)_2$	90	95	$C_{20}H_{19}N_3OS_2$
37	4-FC_6H_4	2-pyridyl	H	H	$(CH_2)_2$	92	106–107	$C_{15}H_{16}FN_3S$
38	4-FC_6H_4	2-pyridyl	OH	H	$(CH_2)_2$	84	148–149	$C_{15}H_{16}FN_3OS$
39[d]	4-FC_6H_4	2-pyridyl		H	$=CHCH_2$	75	155–156	$C_{15}H_{14}FN_3S$
40	2-thienyl	2-pyridyl	H	H	$(CH_2)_2$	93	138	$C_{13}H_{15}N_3S_2$
41[f]	4-FC_6H_4	2-pyridyl	H	H	$(CH_2)_2$	85	91–93	$C_{16}H_{18}FN_3S \cdot HI$
42	4-FC_6H_4	2-pyridyl	OH	H	$(CH_2)_2$	84	114–115	$C_{16}H_{18}FN_3OS \cdot HI$
43[c]	4-FC_6H_4	2-pyridyl		H	$=CHCH_2$	68	139–140	$C_{16}H_{16}FN_3S \cdot 2C_6H_3N_3O_7$
44	4-$MeOC_6H_4$	2-pyridyl	H	H	$(CH_2)_2$	72	123–125	$C_{17}H_{21}N_3OS \cdot HI$
45	2-thienyl	2-pyridyl	H	H	$(CH_2)_2$	85	158	$C_{14}H_{17}N_3S_2 \cdot HI$

[a] Melting points of amorphous solids are in parentheses. [b] All compounds analyzed for C, H, N, except formulas in parentheses. [c] Anal. C, 65.21; H, 5.62; N, 15.21 (Calcd C, 65.16; H, 5.47; N, 15.72). [d] *Z/E* mixture. [e] MS *m/z* 482. [f] Dipicrate: mp 176–177 °C (from EtOH). Anal. ($C_{16}H_{18}FN_3S \cdot 2C_6H_3N_3O_7$) C, H, N.

than histamine on H_2 receptors and, additionally, to be a moderate H_1 antagonist, achieving about 10% the potency of diphenhydramine or pheniramine.

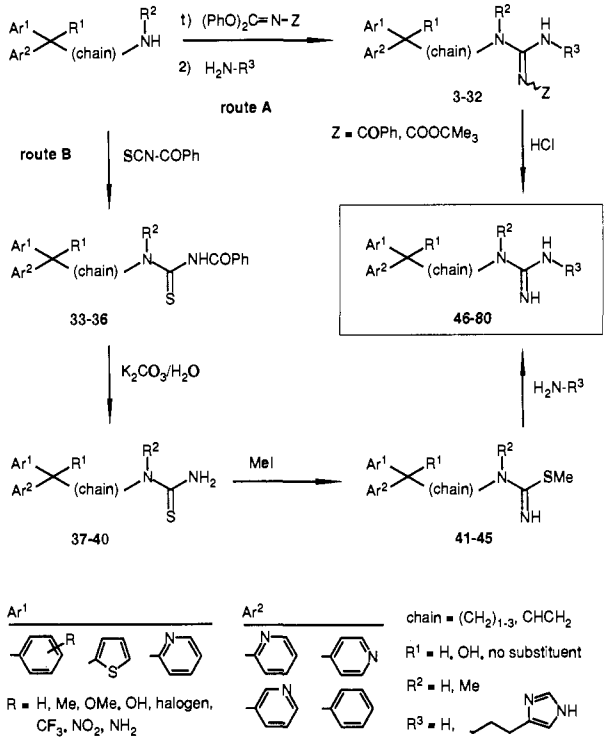
With **2** as the lead structure, the "connecting chain" was modified, e.g., by replacing the thioether link and optimizing the chain length. In addition, the substitution pattern at the phenyl nucleus was varied and the 2-pyridyl group was replaced by alternative rings.

Chemistry

The guanidines were preferably prepared according to route A (Scheme II). The pheniramine-like amines[12] were first treated with diphenyl *N*-benzoylcarbonimidate.[13] Subsequently, without isolation the resulting benzoylisoureas were aminolyzed by refluxing with 3-imidazol-4-ylpropanamine (homohistamine)[14] in acetonitrile or pyridine or, for the preparation of **32**, by stirring with an excess of methanolic ammonia at ambient temperature. The resulting benzoylguanidines (**3–32**) were hydrolyzed in 20% HCl or 48% HBr (preparation of **51** from **7**), affording the guanidines as hygroscopic amorphous hydrohalides. The guanidines **59** and **60** were analogously synthesized via acidic hydrolysis of the corresponding *tert*-butyl guanidine-*N*-carboxylates[15] under mild conditions. Acid-sensitive compounds were prepared via aminolysis of the appropriate *S*-methylisothioureas (route B), which are accessible by addition of the amines to benzoyl isothio-

(11) Buschauer, A. *Sci. Pharm.* **1988**, *56*, 81.
(12) Buschauer, A. *Arch. Pharm. (Weinheim, Ger.)* **1989**, *322*, 165. The preparation of the amines required for the synthesis of guanidines **68**, **72**, and **74** will be published elsewhere.
(13) Buschauer, A. *Arch. Pharm. (Weinheim, Ger.)* **1987**, *320*, 377.
(14) Elz, S.; Schunack, W. *Z. Naturforsch.* **1987**, *42b*, 238.
(15) The preparation of the requisite guanidine-*N*-carboxylates will be published elsewhere.

Scheme II



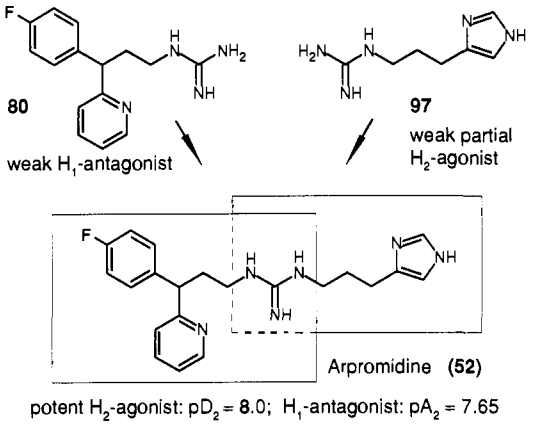
cyanate, followed by alkaline hydrolysis and *S*-methylation. See Table I for the structures and data for the intermediates.

Biological Results and Discussion

The compounds synthesized were screened for H_2 agonism at the isolated spontaneously beating right atrium[16] and, in part, at the electrically stimulated papillary muscle and the isolated perfused heart of the guinea pig. The H_1-antagonistic activity was evaluated at the isolated guinea pig ileum. All compounds investigated are characterized by combined H_2-agonistic and H_1-antagonistic activity (Table II). The structure–activity relationships may be summarized as follows.

Optimization of the Connecting Chain. Bioisosteric replacement of the sulfur atom in the connecting chain of **2** by methylene (**46**) results only in a slight decrease in H_1-antagonistic potency, whereas the H_2-agonistic activity remains unaffected. The crucial structural modification was the shortening of the connecting chain by one methylene group. Guanidine **48** is about 25 times more potent than histamine as an agonist on the atrium. The pA_2 for H_1-antagonistic activity on the ileum corresponds to approximately 10% the potency of diphenhydramine or pheniramine. Further shortening of the chain by one methylene group (**73**) produces a decrease of both activities. Thus, a three-membered carbon chain connecting a phenyl/pyridyl ring and a guanidine group represents the optimum. The H_2-agonistic potency is reduced by 75% when the tertiary carbon in **52** is substituted by an OH group (**68**). About the same decrease in activity is induced by introducing a C=C double bond in the chain (**72**).[17] The guanidino group should only be monosubstituted at both N^1 and N^2. The 2-fold substitution at one guanidine nitrogen as in **69** ($R^2 = CH_3$) is not tolerated and results in a 400-fold decrease in H_2-agonistic potency in comparison with that of **52** (BU-E-50, arpromidine[18]). Similar results are reported for the impromidine series, when the third guanidine nitrogen was methylated.[8]

Scheme III



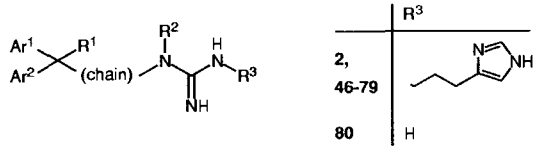
potent H_2-agonist: $pD_2 = 8.0$; H_1-antagonist: $pA_2 = 7.65$

Substitution Pattern of the Phenyl Ring. The H_2-agonistic activity is increased 2–4-fold by ring substitution of the parent molecule **48** with Cl or F in the meta or para position. Other substituents than Cl or F only slightly affect the H_2-agonistic potency, except a *p*-OH group (**51**), which was found to reduce the activity on the atrium by 90%. There is no significant difference between the activity of meta- and para-substituted compounds on the atrium. The ortho-fluorinated (**61**) and ortho-chlorinated compound (**62**) are about as active as **48**, and the para-chlorinated substance **53** and the 2,4-Cl_2-substituted analogue **67** were also found to have similar activities. The ortho-halogen does not seem to confer receptor affinity. But the lack of decrease in activity after ortho substitution in comparison with the corresponding ortho-nonsubstituted compounds indicates that in the active conformation coplanarity of the phenyl ring and connecting chain is unlikely. In the meta/para-disubstituted series steric parameters seem to be involved. Disubstitution in the 3,4-positions with Cl (**65**) or F (**63**) or difluorination in the 3,5-positions (**64**) results in 110–160 times the activity of histamine in the atrium, whereas the analogous 3,5-dichlorinated compound **66** is substantially less potent. In contrast to F, a second Cl atom in the meta position may be too bulky, thus preventing the pheniramine part of the molecule from optimal binding to the receptor. Highest H_1-antagonistic potency in the ileum is found in the para-halogenated series (see **52** vs **56**). Considering both H_1 and H_2 activity, *p*-F represents the optimal substituent. Arpromidine (**52**) combines about 100 times the activity of histamine on the atrium and H_1-antihistaminic activity in the range of pheniramine[19] ($pA_2 = 7.8$). Concerning H_1 antagonism, the order of potency **52** > **53** > **54** is not congruent with that of the related pheniramines. In contrast to **52** "fluorpheniramine"[20] (**96**, pA_2 at the guinea pig ileum: 8.05 ± 0.1) is less potent than its chloro and bromo analogues.[20]

Replacement of the 2-Pyridyl Group. The 2-pyridyl group may be replaced by 3-pyridyl (**74**) without significant change in H_2-agonistic activity, but H_1-antagonistic potency is reduced by 10-fold. The (diarylalkyl)guanidines **76–79** and the 4-pyridyl analogue **75** are 2–4-fold less active in the atrium than the corresponding reference compound

(16) Black, J. W.; Duncan, W. A. M.; Durant, G. J.; Ganellin, C. R.; Parsons, M. E. *Nature (London)* **1972**, *236*, 385.
(17) Guanidine **72** was investigated as a *Z*/*E* mixture, approximately 20/80. Considering the decrease in activity, a separation of the diastereomers was not carried out.
(18) Arpromidine is the proposed INN.
(19) Marshall, P. B. *Br. J. Pharmacol. Chemother.* **1955**, *10*, 270.
(20) Saijo, S. *J. Pharm. Soc. Jpn. (Yakugaku Zasshi)* **1952**, *72*, 1529; *Chem. Abstr.* **1953**, *47*, 8080*i*.

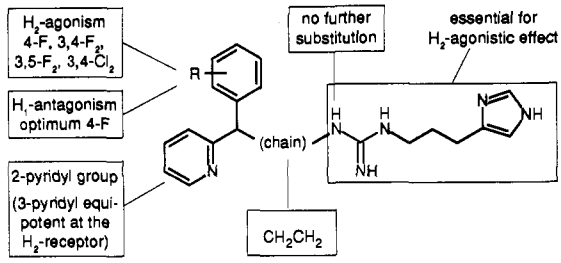
Table II. Structures, Formulas, and Results of the Pharmacological Screening on Isolated Right Atrium, Electrically Stimulated Papillary Muscle, and Isolated Ileum of the Guinea Pig for Guanidines



no.	Ar¹	Ar²	R¹	R²	chain	% yield	mp,[a] °C	formula[b]	atrium (agonism) ia[c]	atrium (agonism) pD_2 ± 0.1[d]	atrium (agonism) n[e]	atrium (agonism) rel potency[f]	papillary muscle (agonism) ia[c]	papillary muscle (agonism) pD_2 ± 0.2[d]	papillary muscle (agonism) n[e]	ileum (antagonism) pA_2 ± 0.1[d]	ileum (antagonism) n[e]	ileum (antagonism) slope ± 0.25[d]
2[g]	Ph	2-pyridyl	H	H	SCH_2CH_2				1.0	6.60		4.0		nd		7.00		
46	Ph	2-pyridyl	H	H	$(CH_2)_3$	93	(82)	$C_{22}H_{28}N_6 \cdot 3C_6H_3N_3O_7 \cdot {}^1/_2H_2O$	1.0	6.61	3	4.1		nd		6.60	4	1.12
47	4-FC_6H_4	2-pyridyl	H	H	$(CH_2)_3$	88	(73)	$C_{22}H_{27}FN_6 \cdot 3C_6H_3N_3O_7 \cdot {}^1/_2H_2O$	0.9	6.87	3	7.4		nd		7.33	5	1.07
48	Ph	2-pyridyl	H	H	$(CH_2)_2$	85	(91)	$C_{21}H_{26}N_6 \cdot 3C_6H_3N_3O_7$	1.0	7.39	3	24.5	0.7	7.37	5	7.01	6	1.29
49	4-MeC_6H_4	2-pyridyl	H	H	$(CH_2)_2$	90	(115)	$C_{22}H_{28}N_6 \cdot 3C_6H_3N_3O_7 \cdot {}^1/_2H_2O$	1.0	7.71	3	51.3	1.0	7.15	3	6.83	4	1.52
50	4-$MeOC_6H_4$	2-pyridyl	H	H	$(CH_2)_2$	72	(84)	$C_{22}H_{28}N_6O \cdot 3C_6H_3N_3O_7 \cdot H_2O$	1.0	7.44	3	27.5	0.5	7.00	3	6.57	4	1.15
51	4-HOC_6H_4	2-pyridyl	H	H	$(CH_2)_2$	85	(90)	$C_{21}H_{26}N_6O \cdot 3C_6H_3N_3O_7 \cdot C_2H_5OH$	1.0	6.63	3	4.3		nd		6.18	4	1.40
52	4-FC_6H_4	2-pyridyl	H	H	$(CH_2)_2$	92	(89)	$C_{21}H_{25}FN_6 \cdot 3C_6H_3N_3O_7 \cdot {}^1/_2H_2O$	1.0	8.01	5	102.3	0.8	7.94	5	7.65	7	1.12
53	4-ClC_6H_4	2-pyridyl	H	H	$(CH_2)_2$	94	(90)	$C_{21}H_{25}ClN_6 \cdot 3C_6H_3N_3O_7$	1.0	7.84	4	69.2	0.8	7.39	3	7.11	8	0.98
54	4-BrC_6H_4	2-pyridyl	H	H	$(CH_2)_2$	89	(94–97)	$C_{21}H_{25}BrN_6 \cdot 3C_6H_3N_3O_7 \cdot {}^1/_2H_2O$	1.0	7.48	3	30.2	0.4	6.97	3	6.92	4	1.41
55	4-$CF_3C_6H_4$	2-pyridyl	H	H	$(CH_2)_2$	88	(88)	$C_{22}H_{25}F_3N_6 \cdot 3C_6H_3N_3O_7$	0.9	7.76	3	57.5	0.9	7.23	3	(6.55)[h,i]	4	
56	3-FC_6H_4	2-pyridyl	H	H	$(CH_2)_2$	88	(78)	$C_{21}H_{25}FN_6 \cdot 3C_6H_3N_3O_7$	1.0	7.88	3	75.9	0.5	7.79	3	6.80	4	1.18
57	3-ClC_6H_4	2-pyridyl	H	H	$(CH_2)_2$	91	(116–117)	$C_{21}H_{25}ClN_6 \cdot 3C_6H_3N_3O_7 \cdot {}^1/_2H_2O$	1.0	7.94	3	87.1	0.6	7.71	3	7.05	4	1.21
58	3-$CF_3C_6H_4$	2-pyridyl	H	H	$(CH_2)_2$	93	(88)	$C_{22}H_{25}F_3N_6 \cdot 3C_6H_3N_3O_7 \cdot {}^1/_2C_2H_5OH$	1.0	7.43	3	26.9	0.7	7.44	4	6.28	4	1.41
59	3-$NO_2C_6H_4$	2-pyridyl	H	H	$(CH_2)_2$	96	(95)	$C_{21}H_{25}N_7O_2 \cdot 3C_6H_3N_3O_7$	0.9	6.91	3	8.1		nd		5.77	6	1.40
60	3-$NH_2C_6H_4$	2-pyridyl	H	H	$(CH_2)_2$	98	*j*	$(C_{21}H_{27}N_7 \cdot 4HCl)^j$	0.9	7.38	3	24.0		nd		6.07	4	0.97
61	2-FC_6H_4	2-pyridyl	H	H	$(CH_2)_2$	90	(79)	$C_{21}H_{25}FN_6 \cdot 3C_6H_3N_3O_7 \cdot {}^1/_2H_2O$	1.0	7.46	3	28.8		nd		6.36	4	0.66
62	2-ClC_6H_4	2-pyridyl	H	H	$(CH_2)_2$	88	(87)	$C_{21}H_{25}ClN_6 \cdot 3C_6H_3N_3O_7 \cdot {}^1/_2H_2O$	0.9	7.35	3	22.4		nd		6.29	4	1.01
63	3,4-$F_2C_6H_3$	2-pyridyl	H	H	$(CH_2)_2$	89	(78)	$C_{21}H_{24}F_2N_6 \cdot 3C_6H_3N_3O_7 \cdot H_2O$	1.0	8.12	4	131.8	0.8	7.90	3	7.07	4	1.51
64	3,5-$F_2C_6H_3$	2-pyridyl	H	H	$(CH_2)_2$	85	(88)	$C_{21}H_{24}F_2N_6 \cdot 3C_6H_3N_3O_7 \cdot {}^1/_2H_2O$	1.0	8.05	3	112.2	0.8	7.91	4	6.56	4	1.40
65	3,4-$Cl_2C_6H_3$	2-pyridyl	H	H	$(CH_2)_2$	91	(109)	$C_{21}H_{24}Cl_2N_6 \cdot 3C_6H_3N_3O_7 \cdot H_2O$	1.0	8.19	5	154.9	0.8	7.54	4	7.10	4	0.95
66	3,5-$Cl_2C_6H_3$	2-pyridyl	H	H	$(CH_2)_2$	86	(104)	$C_{21}H_{24}Cl_2N_6 \cdot 3C_6H_3N_3O_7 \cdot {}^1/_2H_2O$	1.0	7.37	4	23.4		nd		7.36	4	0.79
67	2,4-$Cl_2C_6H_3$	2-pyridyl	H	H	$(CH_2)_2$	92	(110)	$C_{21}H_{24}Cl_2N_6 \cdot 3C_6H_3N_3O_7 \cdot {}^1/_2H_2O$	0.9	7.72	3	52.5		nd		6.54	4	1.08
68	4-FC_6H_4	2-pyridyl	OH	H	$(CH_2)_2$	55	(92)	$C_{21}H_{25}FN_6O \cdot 3C_6H_3N_3O_7 \cdot C_2H_5OH$	0.9	7.42	3	26.3		nd		6.94	4	1.11
69	4-FC_6H_4	2-pyridyl	H	Me	$(CH_2)_2$	91	(80)	$C_{22}H_{27}FN_6 \cdot 3C_6H_3N_3O_7$	0.8	5.40	2	0.25		nd		5.96	4	1.10
70	2-thienyl	2-pyridyl	H	H	$(CH_2)_2$	51	(87)	$C_{19}H_{25}N_6S \cdot 3C_6H_3N_3O_7 \cdot H_2O$	1.0	7.16	3	14.5		nd		7.34	8	0.80
71	2-pyridyl	2-pyridyl	H	H	$(CH_2)_2$	93	165–167[k]	$C_{20}H_{25}N_7 \cdot 4C_6H_3N_3O_7$	1.0	6.90	3	7.9		nd		6.41	4	1.62
72[l]	4-FC_6H_4	2-pyridyl	–	H	$=CHCH_2$	38	(88)	$C_{21}H_{23}FN_6 \cdot 3C_6H_3N_3O_7 \cdot H_2O$	1.0	7.47	3	29.5		nd		6.46	4	1.38
73	Ph	2-pyridyl	H	H	CH_2	94	(105)	$C_{20}H_{24}N_6 \cdot 3C_6H_3N_3O_7 \cdot H_2O$	1.0	6.35	4	2.2		nd		(5.48)[h]	3	
74	4-FC_6H_4	3-pyridyl	H	H	$(CH_2)_2$	89	(96)	$C_{21}H_{25}N_6 \cdot 3C_6H_3N_3O_7 \cdot C_2H_5OH$	1.0	8.09	3	123.0	0.8	7.91	4	6.71	4	0.81
75	4-FC_6H_4	4-pyridyl	H	H	$(CH_2)_2$	88	(77)	$C_{21}H_{25}FN_6 \cdot 3C_6H_3N_3O_7 \cdot {}^1/_2H_2O$	1.0	7.63	3	42.7	0.9	7.28	4	7.43	4	1.23
76	4-FC_6H_4	Ph	H	H	$(CH_2)_2$	92	(73–75)	$C_{22}H_{26}FN_5 \cdot 2C_6H_3N_3O_7$	1.0	7.73	3	53.7	0.7	7.45	4	(7.46)[h]	4	
77	4-ClC_6H_4	Ph	H	H	$(CH_2)_2$	91	(80)	$C_{22}H_{26}ClN_5 \cdot 2C_6H_3N_3O_7$	1.0	7.12	3	13.2	0.8	5.83	3	(7.01)[h]	4	
78	3,4-$Cl_2C_6H_3$	Ph	H	H	$(CH_2)_2$	87	(82)	$C_{22}H_{25}Cl_2N_5 \cdot 2C_6H_3N_3O_7$	1.0	7.46	3	28.8	0.6	6.03	3	(6.71)[h]	4	
79	4-FC_6H_4	benzyl	H	H	$(CH_2)_2$	93	(77)	$C_{23}H_{28}FN_5 \cdot 2C_6H_3N_3O_7 \cdot {}^1/_2H_2O$	0.8	6.17	2	1.5		nd		(6.85)[h]	4	
80	4-FC_6H_4	2-pyridyl	H	H	$(CH_2)_2$	80	239[k]	$C_{15}H_{17}FN_4 \cdot 2C_6H_3N_3O_7$	–	*m*	2	–		nd		(6.64)[h,m]	4	
									1.0	6.00	>50	1.0	1.0	6.25	>30	–		
									1.0	7.70	4	50.1[o]	0.8	7.65[p]	5	5.47[q]		
									–	–	–	–	–	–	–	7.80[r]	8	1.12

[a] Melting points of amorphous solids obtained after drying of the picrates at 50–65 °$C_{0.1}$ are in parentheses. The picrates obtained from EtOH–H_2O as described for **52** in the Experimental Section were purified by tituration with Et_2O–EtOH unless otherwise indicated. [b] All compounds analyzed for C, H, N, except formulas in parentheses. [c] Intrinsic activity, relative to histamine (maximum response = 1). [d] Mean; SEM within the limits indicated. pD_2 values were calculated from cumulative concentration–response curves versus histamine as standard. Nd = not determined. All guanidines tested as hydrohalides. [e] Number of determinations. [f] Potency relative to histamine = 1, calculated from mean pD_2 values. [g] Reference 10. [h] These figures represent $-\log K_B$ obtained at 3 μM concentration of the antagonist from the expression log (DR – 1) = [ant.] $-\log K_B$ since the compounds show a decrease in the maximum effect of histamine at 10 μM. [i] pD_2' = 4.4 (calculation of pD_2' according to ref 31). [j] Very hygroscopic amorphous solid. HR-MS *m/z* 377.232 28 (M^+, $C_{21}H_{27}N_7$, calcd 377.232 79). [k] Crystallized from EtOH–H_2O. [l] *Z/E* mixture (ref 17). [m] Inactive as agonist in concentrations ≤10 μM. Weak H_2-antagonistic effect; at 10 μM about 30% decrease in the maximal effect of histamine; $-\log K_B$ ~5 (n = 2) at 10 μM. [n] pD_2' = 4.7. [o] Relative potency reported to be 48.1 (ref 6 and 8). [p] pD_2 = 7.85 reported (ref 24). [q] Reference 6. [r] pA_2 = 7.82 reported (ref 19).

Scheme IV



52 in the 2-pyridyl series. The order of potency in the series of analogues of **52** depending on Ar^2 is as follows for H_2 agonism and H_1 antagonism, respectively: 2-pyridyl ~ 3-pyridyl > 4-pyridyl ~ phenyl ≫ benzyl, and 2-pyridyl > 4-pyridyl > phenyl > 3-pyridyl ~ benzyl.

Symbiotic Approach. (Imidazolylpropyl)guanidine (**97**, SK&F 91486)[21] is a weak partial H_2 agonist, and the "fluorpheniramine-like" guanidine **80** is a weak H_1 antagonist without agonistic effect on the guinea pig atrium (Scheme III). The combination of both structural parts results in arpromidine (**52**), which is both a very potent H_2 agonist, achieving 100-fold histamine activity, and an H_1 antagonist about 10 times more active than **80**. Thus, the pheniramine moiety provides additional binding to the H_2 receptor and, reversely, the homohistamine group contributes to the H_1-receptor affinity of **52**.

H_2 agonists useful in therapy must be devoid of H_1-agonistic effects. Additional H_1-antagonistic properties might provide benefits, for example, protection against deleterious H_1-mediated histamine effects, due to histamine release under various clinical conditions. Concerning cardiac effects,[22] H_1 receptors are discussed to be involved in arrhythmias, negative inotropism, and coronary spasms.

The crucial structural features of arpromidine-like guanidines are shown in Scheme IV.

Inotropic Activity in Isolated Guinea Pig Heart Preparations. In a previous study on guanidine derivatives containing a pyridine moiety, the positive inotropic response in guinea pig papillary muscle preparations approximately corresponded with the positive chronotropic effects in the isolated guinea pig right atrium,[23] as found for impromidine,[24] too. For most of the compounds listed in Table II, the potencies found in both test models were also in the same range. But some discrepancies between chronotropic and inotropic response in atrium and papillary muscle appeared for compounds with more lipophilic structural parts, such as a bromophenyl or dichlorophenyl substituent in the pheniramine series (**54**, **65**) or the chlorinated (diphenylpropyl)guanidines (**77**, **78**). These differences may be associated with slow distribution of these substances in the papillary muscle preparation, resulting in extended equilibration periods (>30 min) and prolongation of the time required for recording a cumulative concentration–response curve (>3 h), accompanied with slow exhaustion of the organ.

In contrast to these findings, the rank order of potency found in the atrium was in good correlation with the positive inotropic response in the isolated, perfused guinea pig heart. Impromidine and isoproterenol were found to produce about the same maximal response in this test model.[25] The substances listed in Table III proved to be about equieffective with impromidine in increasing maximal LV dp/dt. Comparing the molar ED_{50} values, in analogy to the results from the atrium, showed that 2–3 times the potency of impromidine was achieved with the guanidines **63**–**65**. Except compounds **54** and **57**, the increase in heart rate associated with maximal inotropic response was significantly lower than that produced by impromidine. In vivo (guinea pig) there was no significant positive chronotropic effect after dosage of arpromidine (**52**) in concentrations producing maximal $\Delta LV\ dp/dt$, whereas impromidine induced about 35% increase in heart rate.[26] Thus, the increase in contractility is predominantly based on improved electromechanical coupling.[26] A very important finding is that, in comparison with impromidine, rhythm disturbances were substantially reduced.[25,26] Depending on the lipophilicity of the diaryl structural part, all compounds investigated showed longer duration of action after bolus injection of a single dose into the perfusion stream (e.g., **65** 27.0 ± 3.7 min versus impromidine 6.5 ± 0.9 min).[25]

Table III. Effects of Selected Guanidines on Isolated Perfused Guinea Pig Hearts[a]

substance	Δ LV dp/dt_{max}	relative potency[b]	Δ heart rate	Δ coronary flow
impromidine	100	100	100	100
48	76 ± 4.7	63	70 ± 5.8	121 ± 15.1
49	96 ± 3.8	138	77 ± 12.5	59 ± 8.2
52	97 ± 3.6	146	57 ± 8	143 ± 17.5
53	91 ± 4.0	90	62 ± 7.7	103 ± 16.4
54	93 ± 3.4	61	101 ± 9.6	155 ± 9.1
57	103 ± 6.4	199	96 ± 10.1	79 ± 5.5
63	123 ± 6.1	240	85 ± 11.2	108 ± 16.4
64	129 ± 6.6	244	79 ± 10.8	182 ± 20.5
65	121 ± 7.7	221	62 ± 9.9	128 ± 15.2

[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%.

In contrast to 100-fold activity in the isolated guinea pig atrium, about 1–5 times the activity of histamine was found for **52** in stimulating acid secretion in the isolated mouse stomach and in the anesthetized rat[27] as well as in isolated rat parietal cell preparations ([^{14}C]aminopyrine method).[28] Although the problem of comparing different pharmacological actions across species must be stressed, there is evidence for lower secretory activity in the arpromidine series relative to impromidine (**1**). In comparison, **1** is reported to have about 50-fold (guinea pig atrium) and 16-fold (rat gastric secretion) the potency of histamine.[6] Recently, dissociation of cardiac and gastric effects has been described for guanidines tested versus **1** at the isolated atrium and gastric fundus of the guinea pig.[29] The pheniramine-like compounds listed in Table II are very polar guanidinium salts like **1**. Nevertheless, considering the cimetidine-like moiety of **1** and the pheniramine moiety of compounds like **52**, there are differences in lipophilicity in structural parts, which may be of

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importance for the affinity to the H_2 receptor, for binding to membranes and for penetration. Thus, the relative organ selectivity of pheniramine-like and related H_2 agonists may be reasoned rather by physicochemical differences between the "affinity-conferring" structural parts than by stimulation of putative H_2-receptor subtypes in the heart and stomach. In recent papers,[30] a correlation between lipophilicity and organ selectivity of H_2-antagonists was discussed.

Conclusions

Replacement of the [(5-methylimidazol-4-yl)thio]ethyl group in impromidine by more lipophilic H_2-nonspecific pheniramine-like structures results in a new class of potent H_2 agonists with additional H_1-antagonistic properties. A number of compounds in this series are very potent positive inotropic agents, characterized by a more beneficial profile of action than impromidine. The results suggest possible therapeutic value of these compounds for the management of congestive heart failure.

Experimental Section

Chemistry. Melting points were determined with a Büchi apparatus and are not corrected. Elemental analyses (C, H, N), performed by the analytical department of the Institute for Pharmacy, Berlin, were within ±0.4% of the theoretical values unless otherwise noted. All structures were confirmed by NMR and mass spectroscopy. ^1H NMR spectra were recorded with a Bruker WP 60 (60 MHz) and a Bruker WM 250 (250 MHz) spectrometer, using tetramethylsilane as internal reference. Electron-impact mass spectra (EI) were measured with a Finnigan MAT CH7A (170 °C, 70 eV) and a MAT 711 mass spectrometer (200 °C, 80 eV), fast atom bombardment mass spectra ($^+$FAB, xenon, DMSO/glycerin) were recorded with a Finnigan MAT CH5DF mass spectrometer. Chromatographic separations in a preparative scale were performed with 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).

Primary Amines. The ω-phenyl-ω-pyridin-2-ylalkanamines as well as 3-pyridin-4-yl-3-(2-thienyl)-, 3-(4-fluorophenyl)-3-pyridin-2-yl-, and 3,3-dipyridin-2-yl-1-propanamine were synthesized according to the methods published.[12]

3-(4-Fluorophenyl)-3-pyridin-2-yl-*N*-methyl-1-propanamine (81). A solution of ethyl chloroformate (2.9 mL, 30 mmol) in Et_2O (20 mL) was dropped into a stirred solution of 3-(4-fluorophenyl)-3-(2-pyridyl)-1-propanamine (6.9 g, 30 mmol) in Et_2O (150 mL). When half of the ethyl chloroformate was added, simultaneous dropwise addition of a solution of NaOH (1.6 g, 40 mmol) in water (20 mL) was started. After stirring for 1 h at ambient temperature, the organic layer was separated, washed with water, dried over Na_2SO_4, and concentrated in vacuo. The remaining oil was diluted with absolute THF (30 mL), dropped into a stirred suspension of $LiAlH_4$ (2.28 g, 60 mmol) in THF, and subsequently refluxed for 1 h. The mixture was hydrolyzed with 4 mL of water in THF (15 mL) and 1 mL of 5% NaOH. The inorganic material was filtered and washed with Et_2O, and the combined solutions were evaporated. The remaining oil was distilled, yielding the title compound (4.7 g, 64%) as a colorless oil ($bp_{0.15}$ 117–120 °C). Anal. ($C_{15}H_{17}FN_2$) C, H, N. The maleate was crystallized by mixing ethanolic solutions of equimolar amounts of the base and of maleic acid followed by addition of Et_2O; mp 125–126 °C (EtOH–Et_2O). Anal. ($C_{15}H_{17}FN_2 \cdot C_4H_4O_4$) C, H, N.

3,3-Diphenylpropanamines. Preparation of 3-(4-Fluorophenyl)-3-phenyl-1-propanamine (85). A solution of 4-fluorobenzophenone (20.2 g, 100 mol) in Et_2O–THF was dropped into a freshly prepared solution of ethyltriphenylphosphonium bromide (55.7 g, 150 mmol) and BuLi (87.5 mL of a 1.6 M solution in hexane, 140 mmol) in 300 mL of Et_2O. Subsequently, the mixture was stirred for 1.5 h at ambient temperature. The solid material was filtered, the organic layer was washed with 5% H_2SO_4 and water, dried over Na_2SO_4, concentrated, and distilled in vacuo ($bp_{0.35}$ 90–92 °C), affording a *Z*/*E* mixture (1:1) of 1-(4-fluorophenyl)-1-phenylpropene (**82**) (19.9 g, 89%): MS *m*/*z* 212. Anal. ($C_{15}H_{13}F$) C, 84.40; H, 6.23 (calcd C, 84.88; H, 6.23). Propene **82** was refluxed for 3 h with a suspension of *N*-bromosuccinimide (17.8 g, 100 mmol) in CCl_4 (150 mL) and a catalytic amount of α,α-azadiisobutyronitrile. After removal of the solid material by filtration, potassium phthalimide (19 g, 103 mmol) and 18-crown-6 (2.6 g, 9.8 mmol) were added to the solution and it was stirred for 24 h at ambient temperature. The organic layer was washed with water, dried over Na_2SO_4, and concentrated in vacuo. The residue was crystallized from EtOH, affording *N*-[3-(4-fluorophenyl)-3-phenyl-2-propen-1-yl]phthalimide (**83**) (25.1 g, 75%), mp 127 °C (from EtOH). Anal. ($C_{23}H_{16}FNO_2$) C, H, N. Phthalimide **83** (17.9 g, 50 mmol) was refluxed for 2 h with hydrazine hydrate (3 mL) in EtOH (300 mL). Subsequently, 20% HCl (30 mL) was added, the mixture was stirred for 1 h, and the precipitate was filtered and washed with EtOH repeatedly. After evaporation of the solution and alkalization, (*Z*/*E*)-3-(4-fluorophenyl)-3-phenyl-2-propen-1-amine (**84**) was extracted with CH_2Cl_2. Distillation in vacuo gave 9.66 g (85%) of **84** as an oil: $bp_{0.5}$ 137 °C; MS *m*/*z* 227. Anal. ($C_{15}H_{14}FN$) C, H, N. Propenamine **84** (5.54 g, 20 mmol) was dissolved in EtOH and 1 M HCl (20 mL) and was hydrogenated over 10% Pd–C catalyst (100 mg), affording **85**·HCl (5.1 g, 96%): mp 159–160 °C (from EtOH–Et_2O); MS *m*/*z* 229. Anal. ($C_{15}H_{16}FN \cdot HCl$) C, H, N.

The following were analogously prepared: *N*-[3-(4-chlorophenyl)-3-phenyl-2-propen-1-yl]phthalimide [**86**; yield 73%; mp 115–117 °C (from EtOH). Anal. $C_{23}H_{16}ClNO_2$) C, H, N.], *N*-[3-(3,4-dichlorophenyl)-3-phenyl-2-propen-1-yl]phthalimide [**87**; yield 67%; mp 122–124 °C (from Et_2O). Anal. ($C_{23}H_{15}Cl_2NO_2$) C, H, N.], 1-(4-chlorophenyl)-3-phenyl-2-propen-1-amine hydrochloride [**88**·HCl; yield 88%; mp 196–198 °C (EtOH–Et_2O). Anal. ($C_{15}H_{14}ClN \cdot HCl$) C, H, N.], 3-(3,4-dichlorophenyl)-3-phenyl-2-propen-1-amine hydrochloride [**89**·HCl; yield 91%; mp 203–204 °C (from EtOH–Et_2O). Anal. ($C_{15}H_{13}Cl_2N \cdot HCl$) C, H, N.], 3-(4-chlorophenyl)-3-phenyl-1-propanamine hydrochloride [**90**·HCl; yield 85%; mp 197–199 °C (from EtOH–Et_2O). Anal. ($C_{15}H_{16}ClN \cdot HCl$) C, H, N.], and 3-(3,4-dichlorophenyl)-3-phenyl-1-propanamine hydrochloride [**91**·HCl; yield 90%; mp 188–190 °C (from EtOH–Et_2O–petroleum ether). Anal. ($C_{15}H_{15}Cl_2N \cdot HCl$) C, H, N.].

3-(4-Fluorophenyl)-4-phenyl-1-butanamine (95). 4-Fluoroacetophenone (13.8 g, 100 mmol), paraformaldehyde (4.5 g, 150 mmol), dibenzylamine hydrochloride (23.3 g, 100 mmol) and 1 mL of concentrated HCl were refluxed in EtOH (200 mL) for 2 h. After addition of another portion of paraformaldehyde (4.5 g), the mixture was refluxed for an additional 4 h. The precipitate of 3-(dibenzylamino)-1-(4-fluorophenyl)propanone hydrochloride (**92**) was filtered and recrystallized from EtOH, yielding colorless crystals (29.9 g, 78%), decomposing at 162 °C. Anal. ($C_{23}H_{22}FNO \cdot HCl$) C, H, N. The amino ketone **92**·HCl (19.2 g, 50 mmol) was converted into the free base with 5% NaOH and extracted with Et_2O. The organic layer was dried over Na_2SO_4, concentrated, and dropped into a solution of benzylmagnesium bromide, freshly prepared from benzyl chloride (7.9 g, 60 mmol) and Mg (1.46 g, 60 mmol) in Et_2O (200 mL). After stirring for 2 h, the solution was poured onto a mixture of crushed ice (200 g) and concentrated HCl (30 mL), subsequently basified with aqueous ammonia and extracted with Et_2O. The organic layer was washed with water, dried (Na_2SO_4), and concentrated, affording 4-(dibenzylamino)-2-(4-fluorophenyl)-1-phenyl-2-butanol (**93**) (14.3 g, 65%), mp 95–96 °C (Et_2O). Anal. ($C_{30}H_{30}FNO$) C, H, N. Hydrogenation of **93** (8.8 g, 20 mmol) over 10% Pd–C (120 mg) catalyst after addition of 1 M HCl (20 mL) in EtOH, followed by crystallization from EtOH–Et_2O, afforded 4-amino-2-(4-fluorophenyl)-1-phenyl-2-butanol hydrochloride (**94**) (5.3 g, 90%), mp 204–205 °C. Anal. ($C_{16}H_{18}FNO \cdot HCl$) C, H, N. To a suspension of **94**·HCl (4.7 g, 15.9 mmol) in $CHCl_3$ (100 mL) was added thionyl chloride (1.75 mL, ca. 24 mmol) dropwise with cooling at ambient temperature. The resulting solution was stirred at 50–60 °C for 1 h. The mixture of isomeric dehydration products was isolated by alkalization (5% NaOH), extraction with $CHCl_3$, and evaporation in vacuo. The remaining oil was dissolved in

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EtOH and 1 M HCl (16 mL). Hydrogenation over 10% Pd–C gave crude **95**·HCl. After basification with aqueous NaOH, the free base was extracted with Et_2O and purified by short-path distillation (bath temperature$_{0.5}$ 190–210 °C), affording **95** as a colorless oil (2.5 g, 65%); MS *m/z* 243. For analysis, **95** was crystallized as maleate from EtOH–Et_2O, mp 133–134. Anal. ($C_{16}H_{18}FN \cdot C_4H_4O_4$) C, H, N.

3-(4-Fluorophenyl)-3-pyridin-2-yl-*N*,*N*-dimethyl-1-propanamine[20] (96). A mixture of 3-(4-fluorophenyl)-3-pyridin-2-yl-1-propanamine (2.29 g, 10 mmol), 30% aqueous formaldehyde solution (1.7 mL, 20 mmol), and formic acid (2 mL, ca. 50 mmol) was heated at 100 °C for 1 h. After dilution with water and alkalization with aqueous NaOH, **96** was isolated by extraction with CH_2Cl_2. Short-path distillation (bath temperature$_{1.2}$ 200–210 °C; bp$_7$ 166–169 °C (ref 20)) afforded 2.0 g (78%) of **96** as a colorless oil. The base was converted into the maleate as described above (81) and recrystallized from EtOH–Et_2O, mp 127–128 °C. Anal. ($C_{16}H_{19}FN_2 \cdot C_4H_4O_4$) C, H, N.

Benzoylguanidines. Preparation of N^1-Benzoyl-N^2-[3-(4-fluorophenyl)-3-pyridin-2-ylpropyl]-N^3-[3-(1*H*-imidazol-4-yl)propyl]guanidine (8). A solution of diphenyl *N*-benzoylcarbonimidate (1.59 g, 5 mmol) and 3-(4-fluorophenyl)-3-(2-pyridyl)-1-propanamine (1.24 g, 5 mmol) in dichloromethane (20 mL) was stirred for 30 min at ambient temperature. The solvent was removed under reduced pressure and the oily residue was dissolved in pyridine (30 mL). After addition of 3-(1*H*-imidazol-4-yl)-1-propanamine (0.69 g, 5.5 mmol), the solution was refluxed for 30–60 min (controlled by TLC) and subsequently evaporated in vacuo. The remaining oil was dissolved in 5% HCl and extracted with Et_2O to remove the phenol. After basification with aqueous ammonia, the crude title compound was isolated by extraction with CH_2Cl_2. The organic layer was washed with water, dried over Na_2SO_4, and evaporated in vacuo. The product was purified by chromatography using a Chromatotron (4-mm layers of silica gel PF_{245}, containing gypsum; $CHCl_3$–MeOH 99:1, ammonia atmosphere). After removal of the solvents in vacuo and trituration of the resulting foam with petroleum ether and a few drops of EtOH, **8** was obtained as a colorless amorphous solid (1.41 g, 58%), sintering at 65 °C; $^+$FAB-MS *m/z* (relative intensity) 485 (31, M + H$^+$), 214 (96), 109 (33), 105 (100), 77 (30). Anal. ($C_{28}H_{29}FN_6O$) C, H, N.

Compounds **3–7**, **19–32** (Table I) were prepared in the same way and were obtained either as amorphous solids by trituration with petroleum ether–EtOH or as colorless crystals by crystallization from EtOH–Et_2O (**3**, **4**, **25**, **28**) or EtOAc–Et_2O (**23**).

***N*-Benzoylthioureas. Preparation of N^1-Benzoyl-N^2-[3-hydroxy-3-(4-fluorophenyl)-3-pyridin-2-ylpropyl]thiourea (34).** 3-Amino-1-(4-fluorophenyl)-1-pyridin-2-yl-1-propanol (3.69 g, 15 mmol) and benzoyl isothiocyanate (2.45 g, 15 mmol) were refluxed for 40 min in $CHCl_3$ (150 mL). The solvent was removed in vacuo and **34** (5.4 g, 88%) was crystallized from EtOH–H_2O; mp 138–139 °C. Anal. ($C_{22}H_{20}FN_3O_2S$) C, H, N.

In the same way were prepared **33** (crystallized from Et_2O), **35** and **36** (crystallized from EtOH). The benzoylthiourea required for the synthesis of the *S*-methylisothiourea **44** was isolated as an oil and used directly for further reaction without purification.

Thioureas. *N*-[3-Hydroxy-3-(4-fluorophenyl)-3-pyridin-2-ylpropyl]thiourea (38). Benzoylthiourea **34** (3.07 g, 7.5 mmol) was refluxed for 1 h in a solution of K_2CO_3 (2.1 g) in MeOH–H_2O (70 mL/30 mL). Concentration in vacuo afforded thiourea **38** (1.92 g, 84%) as colorless crystals, mp 148–149 °C (from EtOH–H_2O). Anal. ($C_{15}H_{16}FN_3OS$) C, H, N.

In the same way were prepared thioureas **37** (crystallized from EtOAc–Et_2O), **39** (MeOH), and **40** (EtOH). The thiourea required for the synthesis of the *S*-methylisothiourea **44** was isolated as an oil by extraction with $CHCl_3$ and used directly for further reaction without purification.

***S*-Methylisothioureas. *N*-[3-Hydroxy-3-(4-fluorophenyl)-3-pyridin-2-ylpropyl]-*S*-methylisothiuronium Iodide (42·HI).** Thiourea **38** (1.53 g, 5 mmol) was stirred for 12 h with methyl iodide (0.4 mL) in EtOH (60 mL) at ambient temperature. Compound **42**·HI (yield 1.79 g, 84%) crystallized after concentration in vacuo and trituration of the remaining oil with Et_2O as a colorless solid: mp 114–115 °C (from Me_2CO–Et_2O; crystals dried at 60 °C$_{0.05}$); ^{1}H NMR (DMSO-d_6) δ 2.55 (s, 3 H, SCH_3), 2.62 (m, 1 H, C(OH)C*H*HCH$_2$), 2.77 (m, 1 H, C(OH)CH*H*CH$_2$), 3.23 (m, 2 H, NHC*H*$_2$), 6.21 (s, 1 H, exchangeable, OH), 7.14 (dd, *J* = 8.6, 8.6 Hz, 2 H, Ar*H* ortho to F), 7.29 (m, 1 H, Py-5-H), 7.51 (dd, *J* = 8.6, 5.6 Hz, 2 H, Ar*H* meta to F), 7.64 (d, *J* = 8 Hz, 1 H, Py-3-H), 7.81 (m, 1 H, Py-4-H), 8.54 (m, 1 H, Py-2-H), 9.0 (br, 2 H, exchangeable) and 9.25 (br, 1 H, exchangeable, isothiuronium NH). Anal. ($C_{16}H_{18}FN_3OS$·HI) C, H, N.

In the same way were prepared the hydroiodides of **41**, **43–45** [recrystallization from Me_2CO–Et_2O (**41**·HI, **44**·HI) or EtOH–Et_2O (**45**·HI)]. Isothioureas **41** and **43** were characterized as dipicrates (recrystallization from EtOH–Et_2O).

Guanidines (Route A, Scheme I). N^1-[3-(4-Fluorophenyl)-3-pyridin-2-ylpropyl]-N^2-[3-(1*H*-imidazol-4-yl)-propyl]guanidine (52, Arpromidine). A solution of benzoylguanidine **8** (0.73 g, 1.5 mmol) in 45 mL of 20% HCl was refluxed for 10 h. After dilution with water the benzoic acid was removed by extraction with Et_2O and the aqueous solution was evaporated to dryness under reduced pressure. Drying of the residue in vacuo afforded **52**·3HCl (0.68 g, 92%) as a chromatographically pure, hygroscopic, amorphous solid (foam): ^{1}H NMR (DMSO-d_6) δ 1.83 (m, 2 H, $CH_2CH_2CH_2$), 2.39 (m, 1 H, CHC*H*HCH$_2$), 2.52 (m, 1 H, CHCH*H*CH$_2$), 2.71 (m, 2 H, ImC*H*$_2$), 3.19 (m, 2 H, NHC*H*$_2$), 3.17 (m, 2 H, NHC*H*$_2$), 4.68 (t, *J* = 7.5 Hz, 1 H, ArC*H*), 7.19 (dd, *J* = 8.5, 8.5 Hz, 2 H, Ar*H* ortho to F), 7.49 (s, 1 H, Im-5-H), 7.56 (m, 4 H; 2 Ar*H* meta to F, 2 guanidinium NH, exchangeable), 7.71 (m, 1 H, Py-5-H), 7.95 (m, 3 H, Py-3-H, 2 guanidinium N*H*, exchangeable), 8.29 (m, 1 H, Py-4-H), 8.72 (d, *J* = 5.3 Hz, 1 H, Py-6-H), 9.04 (s, 1 H, Im-2-H), 14.4 (br, 1 H, exchangeable) and 14.8 (br, 1 H, exchangeable, imidazolium NH); $^+$FAB-MS *m/z* (relative intensity) 381 (100, M + H$^+$), 256 (38), 214 (96), 109 (44). For analysis the tripicrate of **52** was formed by addition of an ethanolic solution of picric acid followed by addition of water. The separating oil slowly solidified on stirring for several days. Since recrystallization trials with various solvents were not successful, the tripicrate was purified by dissolution in a small amount of EtOH, addition of Et_2O, and solidification of the resulting oil by trituration. After drying at 60 °C$_{0.1}$, an amorphous solid (**52**) was obtained, mp 89 °C. Anal. ($C_{21}H_{25}FN_6 \cdot 3C_6H_3N_3O_7 \cdot {}^1/_2H_2O$) C, H, N.

The trihydrochlorides of the guanidines **46–49**, **53–58**, **61–67**, **69**, **71**, and **73–75** and the dihydrochlorides of the guanidines **76–80** were prepared in the same way from the appropriate benzoylguanidines. Analogously were prepared compound **51**·3HBr by refluxing benzoylguanidine **7** in 45 mL of 48% aqueous HBr and the guanidines **59**·3HCl and **60**·4HCl by stirring the corresponding *tert*-butyl guanidine-*N*-carboxylates in 1 M HCl at 60–70 °C for 15 min.

Guanidines (Route B, Scheme I). N^1-[3-Hydroxy-3-(4-fluorophenyl)-3-pyridin-2-ylpropyl]-N^2-[3-(1*H*-imidazol-4-yl)propyl]guanidine (68). Compound **42**·HI (1.5 g, 3.5 mmol) and 3-(1*H*-imidazol-4-yl)-1-propanamine (0.48 g, 3.8 mmol) were stirred at 80 °C in pyridine (50 mL) for 5 h. After removal of the volatiles in vacuo, the title compound was isolated and purified by chromatography using a Chromatotron (4-mm layers of silica gel 60 PF_{254} containing gypsum; $CHCl_3$–MeOH, 90:10, ammonia atmosphere) affording 1.0 g (55%) of **68**·HI as amorphous solid. $^+$FAB-MS *m/z* (relative intensity) 397 (89, M + H$^+$), 230 (66), 212 (22), 200 (42), 185 (13), 152 (11), 151 (15), 109 (100), 100 (44), 95 (12). ^{1}H NMR (DMSO-d_6) δ 1.75 (m, 2 H, $CH_2CH_2CH_2$), 2.5–2.9 (m, 4 H, 2 C*H*$_2$), 3.07 (m, 2 H, NHC*H*$_2$), 3.14 (m, 2 H, NHC*H*$_2$), 6.22 (s, 1 H, exchangeable, OH), 6.91 (s, 1 H, Im-5-H), 7.11 (dd, *J* = 8.5, 8.5 Hz, 2 H, Ar*H* ortho to F), 7.27 (m, 1 H, Py-5-H), 7.4 (m, 4 H, exchangeable, guanidinium-NH), 7.52 (dd, *J* = 8.5, 6.8 Hz, 2 H, Ar*H* meta to F), 7.64 (d, *J* = 8 Hz, 1 H, Py-3-H), 7.78 (m, 1 H, Py-4-H), 7.81 (s, 1 H, Im-2-H), 8.53 (m, 1 H, Py-6-H). For analysis the tripicrate of **68** was formed as above, mp 92 °C (amorphous solid, from EtOH–Et_2O). Anal. ($C_{21}H_{25}FN_6O \cdot 3C_6H_3N_3O_7 \cdot C_2H_5OH$) C, H, N.

In the same way were prepared the guanidines **50**·HI, **52**·HI, **70**·HI, and **72**·HI from isothioureas **41** and **43–45**.

For analysis (C, H, N), the guanidines prepared according to route A or B were characterized as picrates analogously as described above (**52**). The resulting salts were usually relatively low-melting, amorphous solids containing persistent polar solvents (EtOH or H_2O), which were very hard to remove by drying.

Pharmacology. For all pharmacological experiments, the substances were used as salts with HCl, HBr (**51**), or HI (**50**, **68**,

70, 72). The investigations on the isolated guinea pig right atrium and ileum were performed according to the experimental conditions previously described.[10] Intrinsic activity, pD_2, and pA_2 were determined from cumulative dose–response curves[31] with histamine dihydrochloride as standard agonist. The incubation time (usually 25 min) after dosage of each single concentration of the guanidines was adapted to the time required for achieving an equilibrium. H_2-receptor selectivity was verified by experiments in presence of cimetidine (10 μM and 1 μM) and metroprolol (1 μM). The positive chronotropic effect in the atrium was not blocked by metoprolol but was competitively antagonized by cimetidine, e.g., the pA_2 value found for cimetidine versus **63** was 6.6 and was not significantly different from the pA_2 found versus histamine (pA_2 = 6.4). The time required for washing out **63** from the tissue after submaximal (ca. 90%) stimulation was over 150 min in comparison with about 25 min for washing out histamine.

The evaluation of the positive inotropic activity on the isolated electrically stimulated (1 Hz, duration 1 ms) guinea pig papillary muscle was performed analogously to a method reported[24] using guinea pig papillary muscles of the right ventricle (Krebs–Henseleit solution, gassed with O_2/CO_2 95:5, bath temperature 32.5 °C). The pD_2 values were calculated from increase in contractile force in cumulative concentration–response curves.

The investigations at isolated perfused, guinea pig hearts (Langendorff technique) followed a procedure described[32] using impromidine as reference compound. The compounds were injected as a bolus directly into the perfusion stream.

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2-[[(4-Amino-2-pyridyl)methyl]sulfinyl]benzimidazole H^+/K^+-ATPase Inhibitors. The Relationship between Pyridine Basicity, Stability, and Activity

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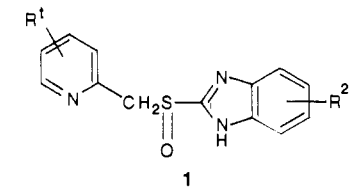
The benzimidazole sulfoxide class of antisecretory H^+/K^+-ATPase inhibitors need to possess high stability under neutral physiological conditions yet rearrange rapidly at low pH to the active sulfenamide **2**. Since the initial reaction involves internal nucleophilic attack by the pyridine nitrogen, control of the pyridine pK_a is critical. In this paper we show that by utilizing the powerful electron-donating effect of a 4-amino substituent on the pyridine, moderated by the electron-withdrawing effect of a 3- or 5-halogen substituent, a combination of high potency (as inhibitors of histamine-stimulated gastric acid secretion) and good stability under physiological conditions can be obtained. Furthermore, the role of the steric interaction between the 3/5-substituents and the 4-substituent in modifying the electron-donating ability of the 4-amino group is exemplified, and additional factors affecting stability are identified. One compound, in particular, 2-[[(3-chloro-4-morpholino-2-pyridyl)methyl]sulfinyl]-5-methoxy-(1*H*)-benzimidazole (**3a**, SK&F 95601), was chosen for further development and evaluation in man.

Inhibition of the proton-pumping H^+/K^+-ATPase as a means of controlling gastric pH has attracted considerable attention in recent years with the discovery of the benzimidazole sulfoxide class of antisecretory agents.[1-3] Such compounds, in particular omeprazole (**1a**), have proved to be effective in the clinic for the treatment of acid-related gastrointestinal disorders. It has been demonstrated that irreversible inhibition of the H^+/K^+-ATPase occurs following acid activation of these compounds within the acidic compartments of the parietal cell and covalent binding of a reactive intermediate to one or more critical thiol groups on the enzyme present in the apical membrane.[5-7]

The chemical transformations that take place at low pH have recently been established and shown to involve an internal rearrangement, initiated by attack of the pyridine nitrogen on the benzimidazole 2-position, followed by a complex cascade of reactions, the cyclic sulfenamide (**2**) being postulated as the principal thiophilic species responsible for activity.[8-11] The direct relationship between the basicity of the pyridine and biological activity previously reported[15,16] can therefore, in part, be accounted for in terms of the increasing reactivity of the parent sulfoxide.

With the aim of identifying compounds combining high potency as inhibitors of histamine-stimulated gastric acid secretion with good stability under physiological conditions, during the course of our work to elucidate the



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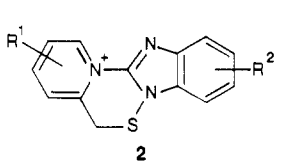

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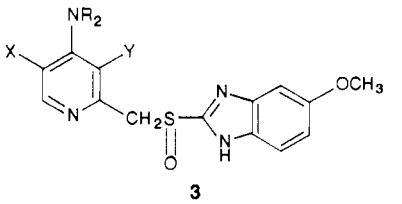
1a (omeprazole): R^2 = 5-OCH_3; R^1 = 3-CH_3, 4-OCH_3, 5-CH_3



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