New Antihistaminic N-Heterocyclic 4-Piperidinamines. 2. Synthesis and Antihistaminic Activity of 1-[(4-Fluorophenyl)methyl]-*N*-(4-piperidinyl)-1*H*-benzimidazol-2-amines

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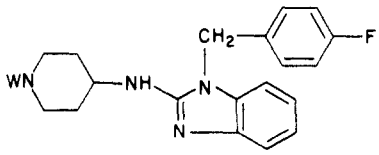
The synthesis of a series of 1-[(4-fluorophenyl)methyl]-*N*-(4-piperidinyl)-1*H*-benzimidazol-2-amines and the preliminary evaluation of their in vivo antihistamine activity are described. The title compounds were obtained starting from either **1**, **4**, **10**, or **55** by different synthetic methods. Substitution on the phenyl nucleus of the benzimidazole ring (**84–87**) was achieved by two different approaches. The in vivo antihistamine activity was evaluated by the compound 48/80 induced lethality test in rats and the antihistamine-induced lethality test in guinea pigs after oral and/or subcutaneous administration. The duration of action was studied in the guinea pig for three compounds (**4**, **51**, and **55**). Compound **51**, "astemizole", was also studied in histamine- and serotonin-induced cutaneous reaction and for mydriatic activity in the rat and tested for peripheral and central effects not related to histamine antagonism in a variety of systems. Astemizole has been selected for clinical investigation.

The discovery of the in vivo antihistamine properties in a series of *N*-(4-piperidinyl)-1*H*-benzimidazol-2-amines[1] prompted us to initiate a broad investigation of structures containing a piperidinylbenzimidazol-2-amine moiety. Previous observations[1] revealed that the 1-benzyl-substituted benzimidazoles, and particularly the 4-fluorobenzyl, preferably in combination with a phenylethyl substituent on the piperidine nitrogen atom (I), possess the most pronounced antihistamine activity.



I

In order to evaluate these previous results, a supplementary series of phenylethyl derivatives and isosteric compounds was prepared. To further define the allowed molecular modifications, more diverse substituents were also introduced, including some on the phenyl nucleus of the benzimidazole ring.

The particular objective of the present investigation was to develop orally active, long-lasting, and selective H_1 antagonists that did not affect the central nervous system.

Chemistry. The majority of compounds, described in this paper, originated from **1** by one of the four following methods (Scheme I): alkylation with alkyl halides or sulfonates in dimethylformamide at 70–90 °C (method A); addition of vinylpyridines in butanol (method B); reductive amination with ketones or aldehydes in methanol (method C); oxirane cleavage in a benzene–methanol mixture (method D). The synthesis of the other compounds is outlined in Schemes II–V.

Acylation of **4** with 4-methoxybenzoyl chloride in the presence of triethylamine afforded **5**. Chlorination of **4** with thionyl chloride yielded **6**, which reacted in dimethylformamide with morpholine to give **7** or **8**, respectively, in the presence or the absence of sodium carbonate (Scheme II, method E).

Hydrogenation of **9** over RaNi yielded the aminoethyl derivative **10**. Reductive amination of the appropriate aldehydes by **10** afforded **11–13**. Methyl isocyanate addition to **10** gave the urea **14**, while acylation with 4-methoxybenzoyl chloride furnished **15** (Scheme III, method F).

The thiophenoxy derivatives **22** and **47**, prepared via method A, were easily oxidized with hydrogen peroxide to the respective sulfones **23** and **48**. Catalytic reduction of the nitro function in **45** furnished the (4-aminophenyl)ethyl derivative **46**.

The (4-hydroxyphenyl)ethyl derivative **55**, efficiently prepared either via hydrobromic acid catalyzed demethylation of **51** or via catalytic debenzylation of **54**, was alkylated with R'Cl in acetone to **56–62**. Acylation, as already illustrated for **5**, afforded **63–67**. Addition of *n*-butyl isocyanate to **55** in tetrahydrofuran yielded the carbamate **68** (Scheme IV, method G).

Substitution on the phenyl nucleus of the benzimidazole ring was achieved by two different approaches (Scheme V). Amination of **77** (R = Cl) with 4-fluorobenzylamine (**76**) in dimethylformamide, followed by nitro reduction with RaNi in methanol, afforded **78** (R = Cl). Addition of the isothiocyanate **79**[1] to the *o*-phenylenediamine **78** (R = Cl) and cyclodesulfurization of the intermediate thiourea yielded **82** (R = Cl). Deprotection of **82** (R = Cl) with 48% aqueous hydrobromic acid solution,[1] followed by alkylation with phenylethyl bromide furnished **84** (R = Cl). In an alternative pathway, **83** (R = F, CH_3) was prepared, starting from the isothiocyanate **79** and the appropriate *o*-phenylenediamine **80** (R = F, CH_3). Cyclodesulfurization of the intermediate thiourea afforded **81** (R = F, CH_3). Alkylation with 4-fluorobenzyl chloride on the *endo*-nitrogen atom[1] of the 2-aminobenzimidazole moiety of **81** (R = F, CH_3) yielded a mixture of **82** (R = F, CH_3) and **83** (R = F, CH_3). Structure elucidation by NMR for the fluoro isomers **82** and **83** was facilitated by comparison with the spectrum of the independently synthesized 5-Cl analogue **82** (R = Cl), prepared from **78** (R = Cl) and **79**.

These mixtures were deprotected and coupled with phenylethyl bromide in dimethylformamide. The 5- and 6-fluoro isomers **85** and **86** were separated via HPLC.

Results and Discussion

The in vivo antihistamine activity was evaluated by the compound 48/80 induced lethality test in rats;[2-4] results are summarized in Tables I and II. Estimated ED_{50} values

(1) Part 1: Janssens, F.; Torremans, J.; Janssen, M.; Stokbroekx, R. A.; Luyckx, M.; Janssen, P. A. J. *J. Med. Chem.*, preceding paper in this issue.

(2) Niemegeers, C. J. E.; Awouters, F.; Van Nueten, J. M.; De Nollin, S.; Janssen, P. A. J. *Arch. Int. Pharmacodyn. Ther.* **1978**, *234*, 164.

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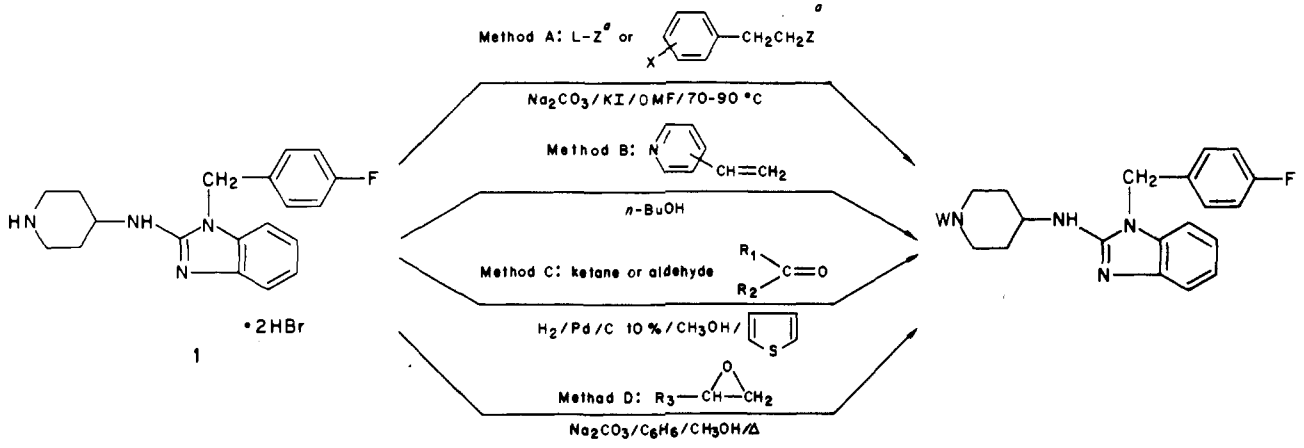
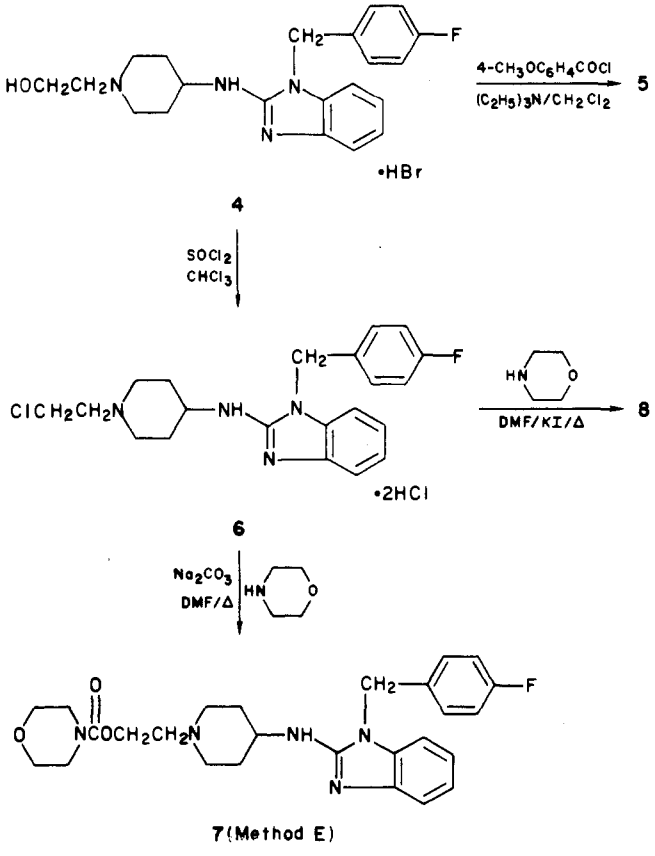
Scheme I

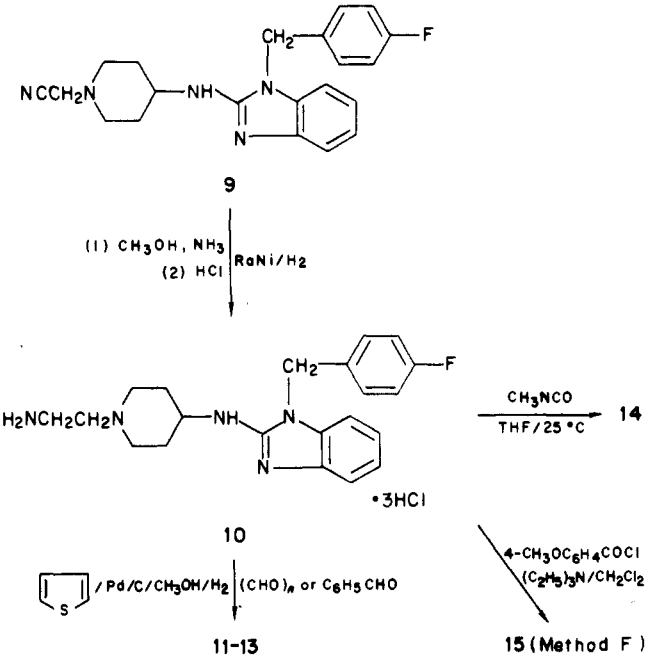


[a] Z = Cl, Br, OSO_2CH_3, $OSO_2C_6H_4CH_3$-4.

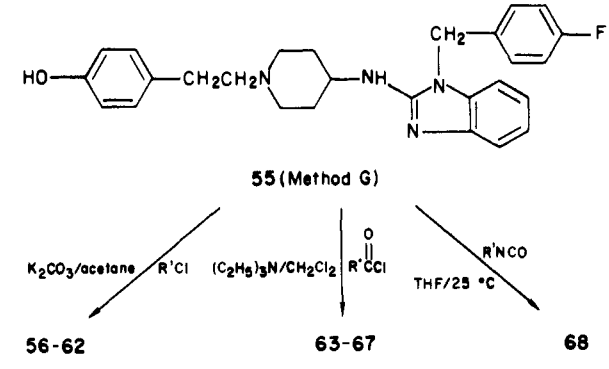
Scheme II



Scheme III



Scheme IV



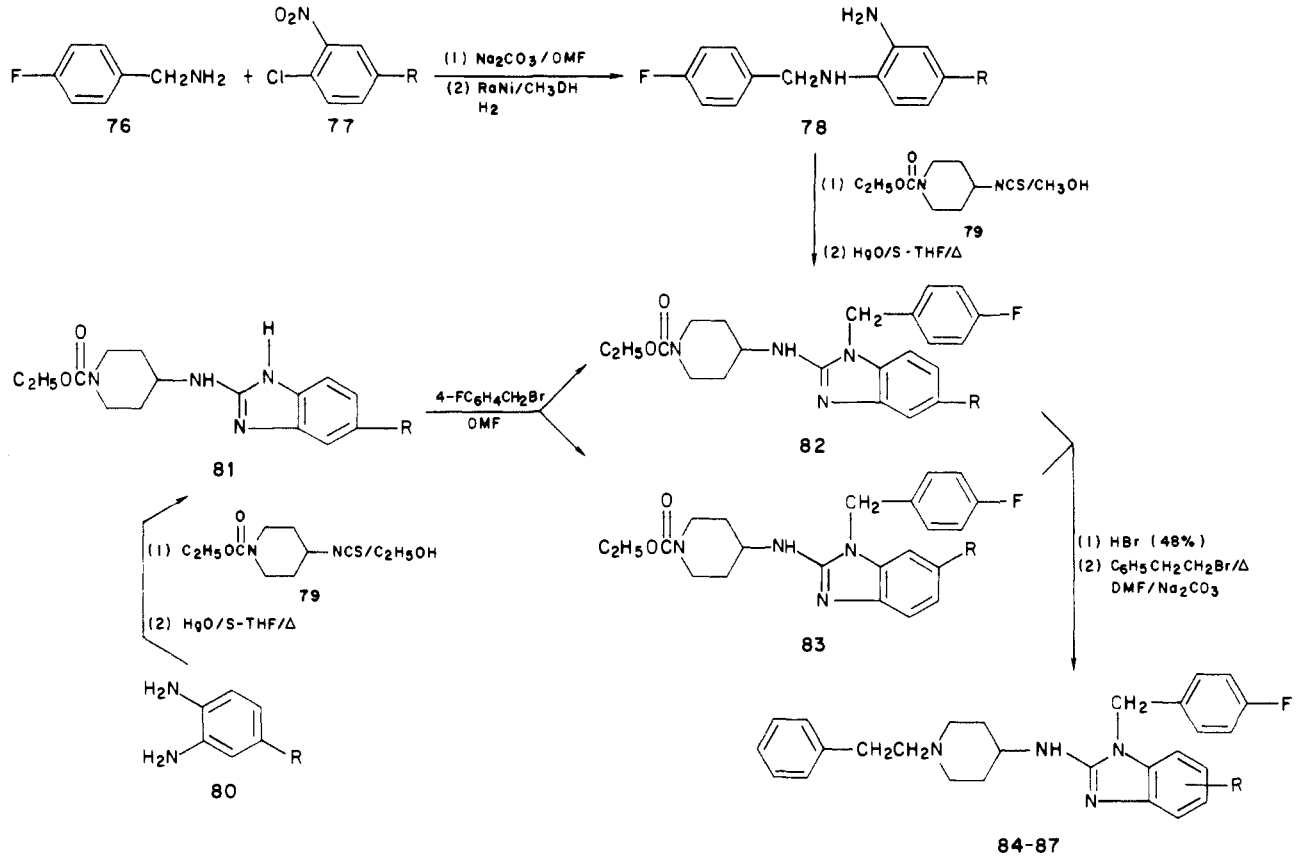
of oxatomide, azatidine, and pyrilamine are included for comparison.

The duration of action for a selected number of compounds was studied in the histamine lethality test in guinea pigs;[5] results are summarized in Table III. Histamine- and serotonin-induced cutaneous reactions tests in rats were performed as already described.[6] The results of these tests together with the compound 48/80 induced lethality and the mydriatic activity in rat for the selected compound **51**, "astemizole", and analogues and four reference compounds are summarized in Table IV.[7]

Evaluating the antihistamine activity in the rat after subcutaneous administration in the compound 48/80 lethality test, maximum activity is found with **4** and **14** (Table I). They are at least twice as potent as **69**, the most

(3) Awouters, F.; Niemegeers, C. J. E.; Janssen, P. A. J. *Drug. Dev. Res.* 1981, *1*, 107.
(4) Awouters, F.; Niemegeers, C. J. E.; Janssen, P. A. J. *Drug. Dev. Res.* 1982, *2*, 559.
(5) Van Wauwe, J.; Awouters, F.; Niemegeers, C. J. E.; Janssens, F.; Van Nueten, J. M.; Janssen, P. A. J. *Arch. Int. Pharmacodyn. Ther.* 1981, *251*, 39.
(6) Awouters, F.; Niemegeers, C. J. E.; Janssen, P. A. J.; Janssen, M.; Vandenberk, J.; Kennis, L.; Van der Aa, M.; Van Heertum, A. In "Drugs Affecting the Respiratory System"; Temple, D. L., Ed.; American Chemical Society: Washington, DC, 1980; Vol 1, pp 179–208.
(7) Niemegeers, C. J. E.; Lenaerts, F. M.; Artois, K. S.; Janssen, P. A. J. *Arch. Int. Pharmacodyn. Ther.* 1977, *227*, 238.

Scheme V



active compound of the phenylethyl derivatives (Table IIA). However, 4 and 14 show reduced oral activity in the rat. Acylation of the alcohol function of 4 does not improve activity, i.e. 5 and 7. With the exception of the urea compound 14, the alkanediamine derivatives (10–15, 18, 20) are inactive or only moderately active. The same is true for the glycidyl (19, 25–29) and (aryloxy)alkyl derivatives (21, 30). The isosteric arylethyl compounds (36–38) are comparable to the (hydroxyphenyl)ethyl derivatives (52, 55, 69) for subcutaneous activity. Di- or trialkoxy substitution usually diminishes subcutaneous effectiveness (72–75).

Analysis of the results of the antihistamine activity in the rat after oral administration in the 48/80 test shows 16 and 30 to be the most potent compounds in the nonphenylethyl series (Table I). Excellent oral activity is observed in the phenylethyl series with the hydroxy- or the alkoxy-substituted derivatives 51, 53, 55, 62–64, 66, 67, 69, and 72. Three of them, i.e. 63, 66, and 67, may be considered as precursors of the (hydroxyphenyl)ethyl derivative 55.

The exceptionally better oral as compared to subcutaneous activity for 16, 25, 30, 49, 53, 55, 62–64, 67, 72, and 75 may probably be associated with the presence of an aryl–alkyl ether bond.[1] Halogen (Cl, F) or methyl substitution (84–87) on the phenyl nucleus of the 2-aminobenzimidazole moiety of 43 obviously reduces the activity following subcutaneous administration. The oral activity decreases with 5-fluoro substitution (85) whereas 6-fluoro substitution (86) has no influence.

The duration of the antihistamine activity for 4, 51, and 55 was evaluated in the histamine lethality test in the guinea pig. While 4 has a very quick onset of action (peak effect after 3 h), 51 and 55 reach their maximum effect 48 and 24 h, respectively, after oral administration. The protective activity after 96 h is significantly reduced for 4, while 51 and 55 still possess a considerable potency. On the basis of the 8-h results, 4 and 55 are as potent as azatadine and more effective than cyproheptadine and oxatomide. However, on the basis of the 24-h results, 4, 51, and 55 exceed the potency of azatadine by factors 15, 19, and 22, respectively.

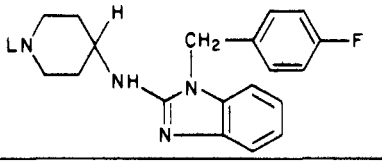
Astemizole (51), selected for further clinical studies, was also compared with reference compounds for protection from 48/80 lethality, inhibition of histamine- and serotonin–skin reaction, and mydriatic activity in rats. With respect to protection from 48/80 lethality and to the inhibition of histamine–skin reactions, 51 significantly surpasses the activity of the reference compounds. In the serotonin–skin reaction 51 is more effective than azatadine but clearly less potent than cyproheptadine. Mydriatic activity for 51 is only observed at 1454 times the effective dose in the compound 48/80 lethality test, while this ratio is only 8 and 11, respectively, for azatadine and cyproheptadine (Table IV).

Compound 51 also demonstrated high potency in vitro at inhibiting histamine-induced contractions (mediated by H_1-histamine receptors) in isolated guinea pig ileum [50% effective concentration (EC_{50}) = 0.0001 mg/L]. However, much higher drug concentrations were required to inhibit histamine-induced increases in the contraction rate of guinea pig atrium (EC_{50} > 0.63 mg/L) and in the acid secretion of rat stomach (EC_{50} > 10.0 mg/L), both of which are mediated by H_2-histamine receptors.[8]

Astemizole (51) was also tested for peripheral and central effects not related to histamine antagonism in a variety of test systems.[9-13] High doses of 51 (results not shown) fail to interfere with animal behaviour or to alter the intensity or duration of action of diverse agents inducing

(8) Awouters, F. H. L.; Niemegeers, C. J. E.; Janssen, P. A. J. *Arzneim.-Forsch.* **1983**, *33*, 381.
(9) Janssen, P. A. J.; Niemegeers, C. J. E.; Schellekens, K. H. L. *Arzneim-Forsch.* **1965**, *15*, 104.

Table I



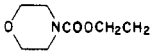
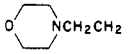
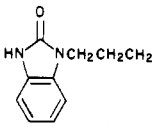
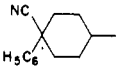
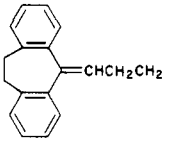
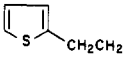
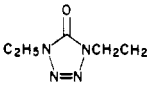
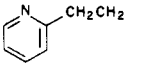
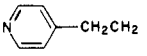
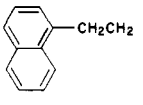
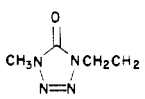
compd	L	formula	mp, °C	yield,[a] %	cryst[b] solv	anal.	meth-od	compd 48/80 lethality test in rats:[c] ED_{50}, mg/kg sc 1 h	oral 2 h
1	H	$C_{19}H_{21}FN_4 \cdot 2HBr \cdot 0.5H_2O$	>260	82	A	C, H, N, Br	*e*	0.056	1.02
2	CH_3	$C_{20}H_{23}FN_4$	145.5	34	D-E	C, H, N, F	C[e]	0.16	2.5
3		$C_{25}H_{31}FN_4$	168.0	57	A-E	C, H, N, F	C	0.31	>2.5
4	$HOCH_2CH_2$	$C_{21}H_{25}FN_4O \cdot HBr$	248.2	64	F	C, H, N, Br, F	D[e]	0.04	0.63
5	$4\text{-}CH_3OC_6H_4COOCH_2CH_2$	$C_{29}H_{31}FN_4O_3 \cdot 2HCl \cdot 0.5H_2O$	189.2	43.5	D	C, H, N, Cl	E[f]	0.31	0.63
6	$ClCH_2CH_2$	$C_{21}H_{24}ClFN_4 \cdot 2HCl$	>260	83	*d*	C, H, N, Cl	E	–	–
7		$C_{26}H_{32}FN_5O_3$	144.8	12.5	D-E	C, H, N, F	E	0.31	2.5
8		$C_{25}H_{32}FN_5O \cdot 3HCl$	300	18.3	B	C, H, N, Cl	E	0.31	2.5
9	$NCCH_2$	$C_{21}H_{22}FN_5$	178.7	55	C-E	C, H, N	A[e]	0.16	2.5
10	$H_2NCH_2CH_2$	$C_{21}H_{26}FN_5 \cdot 3HCl$	292.9	92.3	B-D	C, H, N, Cl	F[g]	1.25	>2.5
11	$(CH_3)_2NCH_2CH_2$	$C_{23}H_{30}FN_5$	166.1	42	D-E	C, H, N, F	F	0.63	2.5
12	$(C_6H_5CH_2)_2NCH_2CH_2$	$C_{35}H_{38}FN_5$	116.4	27.5	D-E	C, H, N, F	F	>2.5	–
13	$C_6H_5CH_2NHCH_2CH_2$	$C_{28}H_{32}FN_5$	135.6	31	E	C, H, N, F	F	1.25	>2.5
14	$CH_3NHCONHCH_2CH_2$	$C_{23}H_{29}FN_6O \cdot H_2O$	231.4	70.7	*d*	C, H, N, F	F	0.02	>2.5
15	$(4\text{-}CH_3OC_6H_4CO)_2NCH_2CH_2$	$C_{37}H_{38}FN_5O_4 \cdot 2HCl \cdot 2H_2O$	161.5	13.4	A	C, H, N, Cl, F	F	>2.5	–
16	$C_6H_5OCH_2CH_2CH_2$	$C_{28}H_{31}FN_4O$	144.5	22	D-E	C, H, N, F	A	1.25	0.31
17		$C_{29}H_{31}FN_6O$	237.6	40	D	C, H, N, F	A	0.31	1.25
18	$4\text{-}FC_6H_4CONHCH_2CH_2$	$C_{28}H_{29}F_2N_5O$	193.7	19	D-E	C, H, N, F	A	0.31	2.5
19	$C_6H_5OCH_2CH(OH)CH_2$	$C_{28}H_{31}FN_4O_2$	181.3	32	A	C, H, N, F	D	0.63	1.25
20	$C_6H_5NHCH_2CH_2CH_2$	$C_{28}H_{32}FN_5$	153.1	35	E	C, H, N, F	A	0.63	2.5
21	$C_6H_5OCH_2CH_2CH_2CH_2$	$C_{29}H_{33}FN_4O$	150.7	17	D	C, H, N, F	A	0.63	0.63
22	$4\text{-}CH_3OC_6H_4SCH_2CH_2CH_2$	$C_{29}H_{34}FN_4OS$	114.5	–	D-E	C, H, N	A	2.5	–
23	$4\text{-}CH_3OC_6H_4SO_2(CH_2)_3$	$C_{29}H_{33}FN_4O_3S \cdot 2C_2H_2O_4$	213.1	16	A-B	C, H, N, F	*h*	0.31	2.5
24		$C_{32}H_{34}FN_5 \cdot 2HCl$	275	34	D	C, H, N, F, Cl	C	>2.5	–
25	$2\text{-}CH_3OC_6H_4OCH_2CH(OH)CH_2$	$C_{29}H_{33}FN_4O_3$	174	40	A	C, H, N, F	D	1.25	0.63
26	$4\text{-}CH_3OC_6H_4OCH_2CH(OH)CH_2$	$C_{29}H_{33}FN_4O_3$	174.5	51	D-E	C, H, N, F	D	1.25	2.5
27	$2\text{-}C_4H_9OC_6H_4OCH_2CH(OH)CH_2$	$C_{32}H_{39}FN_4O_3$	138.7	36	A-E	C, H, N, F	D	2.5	–
28	$4\text{-}CH_3COC_6H_4OCH_2CH(OH)CH_2$	$C_{30}H_{33}FN_4O_3$	174.7	35	A	C, H, N, F	D	0.63	1.25
29	$2,6\text{-}(CH_3O)_2C_6H_3OCH_2CH(OH)CH_2$	$C_{30}H_{35}FN_4O_4$	140.0	47	A	C, H, N, F	D	0.63	1.25
30	$4\text{-}CH_3OC_6H_4OCH_2CH_2CH_2$	$C_{29}H_{33}FN_4O_2$	143.1	41	A-E	C, H, N	A	0.31	0.31
31		$C_{37}H_{37}FN_4$	177.6	36	A-E	C, H, N	A	>2.5	–
32	$C_6H_5CH(CH_3)$	$C_{27}H_{29}FN_4$	182	47	D	N, F	A	0.31	2.5
33	$C_6H_5CH_2CH(CH_3)$	$C_{28}H_{31}FN_4$	182.4	25	D-E	C, H, N, F	C	2.5	–
34	$C_6H_5CH(CH_3)CH_2$	$C_{28}H_{31}FN_4 \cdot 2HNO_3 \cdot 2H_2O$	155.4	23	D	C, H, N, F	A	0.63	2.5
35	$C_6H_5CH{=}CHCH_2$	$C_{28}H_{29}FN_4 \cdot H_2O$	155.5	23	D-E	C, H, N, F	A	1.25	>2.5
36		$C_{25}H_{27}FN_4S$	151.6	53	A	C, H, N, F, S	A	0.16	0.63
37		$C_{24}H_{29}FN_8O$	146.5	48	A-E	C, H, N, F	A	0.16	>2.5
38		$C_{26}H_{28}FN_5$	133.4	23	E	C, H, N, F	B[e]	0.16	0.63
39		$C_{26}H_{28}FN_5$	158.2	35	C	C, H, N, F	B	0.31	1.25
40		$C_{31}H_{31}FN_4$	143.1	42	D	C, H, N, F	A	1.25	0.63

Table I (Continued)

compd	L	formula	mp, °C	yield,[a] %	cryst[b] solv	anal.	method	compd 48/80 lethality test in rats:[c] ED_{50}, mg/kg sc 1 h	compd 48/80 lethality test in rats:[c] ED_{50}, mg/kg oral 2 h
41		$C_{23}H_{27}FN_8O \cdot 2HCl \cdot H_2O$	192.9	19	A–E	C, H, N, Cl	A	0.31	>2.5
42	$C_6H_5CH(OH)CH_2$	$C_{27}H_{29}FN_4O$	184.1	23	A	C, H, N, F	D	0.63	>2.5

[a] Based on immediate precursor, after recrystallization. Generally no attempts made to optimize yields. [b] Key: A = 2-propanol; B = methanol; C = 4-methyl-2-pentanone; D = acetone; E = diisopropyl ether; F = water. [c] The estimated ED_{50} values are used whenever possible so that a comparison of the relative potencies can be made. For inactive compounds the highest dose tested is indicated preceding the symbol > (greater than). Compounds that are not tested are designated with the symbol –. [d] Collected from reaction solvent, not crystallized. [e] See Scheme I. [f] See Scheme II. [g] See Scheme III. [h] Prepared via hydrogen peroxidation of **22**.

CNS effects. In dogs the EEG and sleep–wake patterns do not reveal any changes indicative of stimulant or sedative effects.[14] Clinical observations in allergic patients suggest no somnolence or impairment of concentration.[15-20]

From these data, it can be concluded that astemizole (**51**) is a potent, long-lasting, and selective H_1-antagonist, devoid of central and anticholinergic effects.

Experimental Section

Melting points were determined with a Mettler FP_1 melting point apparatus and are uncorrected. Elemental analyses were performed by the Analytical Department of Janssen Pharmaceutica Laboratories. Mass spectra were measured with a Varian Mat 311-eV emission spectrometer. NMR spectra were measured with either a Brucker HX 60-12 or a Brucker WP 80-DS instrument (internal standard Me_4Si). UV and/or IR spectra were determined with Beckman DK-2A and a Perkin-Elmer 421 or 225 spectrometer. Analytical TLC was performed on silica 60 F_{254} (Merck), and the spots were made visible by a UV lamp or iodine vapor.

1-[(4-Fluorophenyl)methyl]-4-(4-piperidinyl)-1*H*-benzimidazol-2-amine Dihydrobromide (1). (i) A mixture of ethyl 4-(1*H*-benzimidazol-2-ylamino)-1-piperidinecarboxylate (5.6 g, 0.02 mol),[1] 4-fluorobenzyl chloride (2.9 g, 0.02 mol), sodium carbonate (2 g, 0.02 mol), and potassium iodide (0.1 g) in dimethylformamide (200 mL) was stirred overnight at 70 °C. The mixture was poured into water and extracted twice with toluene. The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo, and the residue was triturated with a mixture of 4-methyl-2-pentanone and diisopropyl ether to yield ethyl 4-[[1-[(4-fluorophenyl)-methyl]-1*H*-benzimidazol-2-yl]amino]-1-piperidinecarboxylate: 3.2 g (40%); mp 180.8 °C. Anal. ($C_{22}H_{25}FN_4O_2$) C, H, N, F.

(ii) A solution of ethyl 4-[[1-[(4-fluorophenyl)methyl]-1*H*-benzimidazol-2-yl]amino]-1-piperidinecarboxylate (3.2 g, 0.008 mol) in 48% hydrobromic acid (200 mL) was stirred and refluxed for 1 h. The solvent was evaporated in vacuo, and the residue was crystallized from 2-propanol to afford **1**: 3.3 g (82%); mp 260 °C. Anal. ($C_{19}H_{21}FN_4 \cdot 2HBr \cdot {}^1/_2H_2O$) C, H, N, Br, H_2O.

***N*-(1-Cyclohexyl-4-piperidinyl)-1-[(4-fluorophenyl)-methyl]-1*H*-benzimidazol-2-amine (3).** A solution of **1** (free base) (5.2 g, 0.016 mol) and cyclohexanone (3 g, 0.03 mol) in methanol (150 mL) was hydrogenated over Pd/C (10%, 1 g) at room temperature. The catalyst was poisened by adding 1 mL of a 4% solution of thiophene in methanol (v/v). After uptake of 1 equiv of hydrogen, the catalyst was filtered off, the solvent was evaporated, and the residue was crystallized from 2-propanol–diisopropyl ether to yield **3**: 3.7 g (57%); mp 168.0 °C. Anal. ($C_{25}H_{31}FN_4$) C, H, N, F.

4-[[1-[(4-Fluorophenyl)methyl]-1*H*-benzimidazol-2-yl]-amino]-1-piperidineethanol Monobromide (4). A solution of **1** (40.4 g, 0.1 mol) in methanol was basified with ammonia. After evaporation in vacuo, ethylene oxide (8.8 g, 0.2 mol) in methanol (500 mL) was added and the solution was stirred overnight at room temperature. The solvent was evaporated in vacuo, and the residue was triturated with water to yield **4**: 29 g (64%); mp 248.2 °C. Anal. ($C_{21}H_{25}FN_4O \cdot HBr$) C, H, N, Br, F.

2-[4-[[1-[(4-Fluorophenyl)methyl]-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl 4-Methoxybenzoate Dihydrochloride Hemihydrate (5). A solution of 4-methoxybenzoyl chloride (1.7 g, 0.01 mol) in dichloromethane (50 mL) was added dropwise to a suspension of **4** (4.5 g, 0.01 mol) and triethylamine (2 g, 0.02 mol) in dichloromethane (100 mL) at room temperature. The mixture was kept 24 h at 25 °C and poured into water, and the organic layer was separated. After extraction with CH_2Cl_2 the combined organic layers were dried ($MgSO_4$), filtered, and evaporated. The residue was purified on a silica column (eluent $CHCl_3$–CH_3OH 98:2 (v/v)). The product was collected, the solvent was removed, and the solid residue was acidified with hydrogen chloride in acetone to yield **5**: 2.5 g (43.5%); mp 189.2 °C. Anal. ($C_{29}H_{31}FN_4O_3 \cdot 2HCl \cdot {}^1/_2H_2O$) C, H, N, Cl, H_2O.

***N*-[1-(2-Chloroethyl)-4-piperidinyl]-1-[(4-fluorophenyl)-methyl]-1*H*-benzimidazol-2-amine Dihydrochloride (6).** A solution of the dihydrochloride salt of **4** (15 g, 0.034 mol) and thionyl chloride (4 g, 0.034 mol) was stirred and refluxed in chloroform (250 mL) for 24 h. The solid was collected and dried in vacuo to yield **6**: 13 g (83%); mp >260 °C. Anal. ($C_{21}H_{24}ClFN_4 \cdot 2HCl$) C, H, N, Cl.

2-[4-[[1-[(4-Fluorophenyl)methyl]-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl 4-Morpholinecarboxylate (7). A suspension of **6** (4.8 g, 0.01 mol), morpholine (0.9 g, 0.01 mol), sodium carbonate (3.18 g, 0.03 mol), and potassium iodide (0.1 g) in dimethylformamide (100 mL) was stirred at 70 °C for 20 h. The cooled reaction mixture was extracted twice with toluene. The combined organic layers were dried ($MgSO_4$) and evaporated. The residue was purified on silica (eluant $CHCl_3$–CH_3OH 98:2 (v/v)). The pure fraction was collected and crystallized from a mixture of acetone and diisopropyl ether to yield **7**: 0.6 g (12.5%); mp 144.8 °C. Anal. ($C_{26}H_{32}FN_5O_3$) C, H, N, F.

1-[(4-Fluorophenyl)methyl]-*N*-[1-[2-(4-morpholinyl)-ethyl]-4-piperidinyl]-1*H*-benzimidazol-2-amine Trihydrochloride (8). A solution of **6** (4.8 g, 0.01 mol) and morpholine (3.6 g, 0.04 mol) in dimethylformamide (150 mL) was stirred overnight at 70 °C. The reaction mixture was cooled, poured into

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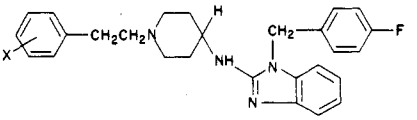
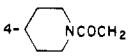
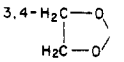
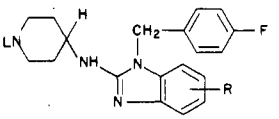
Table II



compd	X	formula	mp, °C	yield,[a] %	cryst[b] solv	anal.	method	compd 48/80 lethality test in rats:[c] ED_{50}, mg/kg, sc sc 1 h	compd 48/80 lethality test in rats:[c] ED_{50}, mg/kg, sc oral 2 h
43	H	$C_{27}H_{29}FN_4 \cdot 2HCl$	271.5	70	A	C, H, N, Cl	A	0.31	0.63
44	4-F	$C_{27}H_{28}F_2N_4 \cdot 2HCl \cdot 0.5H_2O$	283.7	77	D	C, H, N, F	A	0.31	>2.5
45	4-NO_2	$C_{27}H_{28}FN_5O_2$	162.7	53	A	C, H, N	A	>2.5	*c*
46	4-NH_2	$C_{27}H_{30}FN_5$	195.4	42	A	C, H, N, F	*d*	0.31	0.63
47	4-CH_3S	$C_{28}H_{31}FN_4S$	176	32	D	C, H, N	A	0.63	1.25
48	4-CH_3SO_2	$C_{29}H_{31}FN_4O_2S \cdot 0.5C_3H_8O$	235.8	16	A	C, H, N	*e*	1.25	>2.5
49	2-CH_3O	$C_{28}H_{31}FN_4O$	158.1	41	A	C, H, N, F	A	1.25	0.63
50	3-CH_3O	$C_{29}H_{31}FN_4O \cdot 2HCl \cdot 0.5H_2O$	242.4	28	D	C, H, N, Cl	A	0.31	0.31
51	4-CH_3O	$C_{28}H_{31}FN_4O$	171.4	48	E	C, H, N, F	A	0.11	0.11
52	3-OH	$C_{27}H_{29}FN_4O \cdot 2HCl \cdot H_2O$	209.8	9	D	C, H, N, F	A	0.16	0.31
53	4-C_2H_5O	$C_{29}H_{33}FN_4O$	152.3	15	D-E	C, H, N	A	1.25	0.16
54	4-$C_6H_5CH_2O$	$C_{34}H_{35}FN_4O$	155.4	46.7	D-E	C, H, N, F	A	2.5	-
55	4-OH	$C_{27}H_{29}FN_4O$	111.6	88.5	E	C, H, N	G	0.16	0.10
56	4-CH_2=$CHCH_2O$	$C_{30}H_{33}FN_4O \cdot 2HCl \cdot H_2O$	224.7	19.9	D	C, H, N, F	G	2.5	-
57	4-CH_3OOCCH_2O	$C_{30}H_{33}FN_4O_3$	109.8	32	D-E	C, H, N, F	G	2.5	-
58	4-$C_2H_5OOCCH_2O$	$C_{31}H_{35}FN_4O_3$	109.1	37.7	D-E	C, H, N, F	G	0.16	>2.5
59	4-H_2NCOCH_2O	$C_{29}H_{32}FN_5O_2$	180.4	29.6	A	C, H, N, F	G	1.25	2.5
60	4-$C_2H_5NHCOCH_2O$	$C_{31}H_{36}FN_5O_2$	160.9	19	A	C, H, N	G	1.25	2.5
61	4- 	$C_{34}H_{40}FN_5O_2 \cdot 2HCl$	247	43.5	A	C, H, N, Cl	G	1.25	1.25
62	4-$NCCH_2O$	$C_{29}H_{30}FN_5O \cdot 2HCl \cdot H_2O$	224.6	78.6	D	C, H, N	G	0.63	0.08
63	4-$C_6H_5CH_2COO$	$C_{35}H_{35}FN_4O_2$	135.1	18	A	C, H, N, F	G	0.31	0.08
64	4-$CH_3OC_6H_4COO$	$C_{35}H_{35}FN_4O_3$	157.1	17	D-E	C, H, N, F	G	0.63	0.16
65	4-CH_3NHCOO	$C_{29}H_{32}FN_5O_2$	172.2	20	D-E	C, H, N, F	G	1.25	2.5
66	4-$CH_3OC(O)O$	$C_{29}H_{31}FN_4O_3$	134.5	20	D-E	C, H, F	G	0.16	0.16
67	4-$C_6H_5CH_2OC(O)O$	$C_{35}H_{35}FN_4O_3$	147.8	43	A	C, H	G	0.31	0.16
68	4-*n*-C_4H_9NHCOO	$C_{32}H_{38}FN_5O_2$	142.5	18	D-E	C, H, N, F	G	2.5	-
69	4-HO, 3-CH_3	$C_{28}H_{31}FN_4O \cdot 2HCl \cdot H_2O$	277.8	76	D	C, H, N, Cl, F	A	0.08	0.16
70	4-$C_6H_5CH_2O$, 3-CH_3	$C_{35}H_{37}FN_4O$	145.6	36.5	A	C, H, F	A	>2.5	-
71	2,4-$(CH_3O)_2$	$C_{29}H_{33}FN_4O_2 \cdot 2HCl \cdot 0.5H_2O$	190.4	9	D-E	C, H, N, Cl, F	A	0.31	0.31
72	3,4-$(CH_3O)_2$	$C_{29}H_{33}FN_4O_2$	69.3	20	D-E	C, H, N, F	A	1.25	0.16
73	2,5-$(CH_3O)_2$	$C_{29}H_{33}FN_4O_2$	127.9	20	D-E	C, H, N, F	A	0.63	0.63
74	3,4- 	$C_{29}H_{31}FN_4O_2 \cdot 2HCl \cdot H_2O$	264.6	26.8	D	C, H, N, Cl, F	A	1.25	2.5
75	3,4,5-$(CH_3O)_3$	$C_{30}H_{35}FN_4O_3 \cdot 2HCl \cdot 0.5H_2O$	260.2	25	D	C, H, N	A	1.25	0.63
oxatomide								-	5.37 (4.34–6.65)[f]
azatadine								0.049 (0.036–0.066)[f]	0.48 (0.32–0.70)[f]
pyrilamine								-	56.6 (46.0–69.8)[f]



compd	L	R	formula	mp, °C	yield,[g] %	crystn[h] solv	anal	compd 48/80 lethality test in rats:[i] ED_{50}, mg/kg sc -1 h	compd 48/80 lethality test in rats:[i] ED_{50}, mg/kg oral -2 h
82	C_2H_5OOC	5-Cl	$C_{22}H_{24}ClFN_4O_2$	215.8	46.5	C-E	C, H, N, Cl, F	*c*	-
82, 83	C_2H_5OOC	5(6)-F	$C_{22}H_{24}F_2N_4O_2$	182.5	62.1	D-E	C, H, N, F	-	-
82, 83	C_2H_5OOC	5(6)-CH_3	$C_{23}H_{27}FN_4O_2$	173.3	69	D-E	C, H, N, F	-	-
84	$C_6H_5CH_2CH_2$	5-Cl	$C_{27}H_{28}ClFN_4$	168.3	30.2	D-E	C, H, N, Cl, F	>2.5	-
85	$C_6H_5CH_2CH_2$	5-F	$C_{27}H_{28}F_2N_4 \cdot H_2O$	178.1	17.5	E	C, H, N, F	1.25	>2.5
86	$C_6H_5CH_2CH_2$	6-F	$C_{27}H_{28}F_2N_4$	188.8	24.4	E	C, H, N, F	1.25	0.63
87	$C_6H_5CH_2CH_2$	5(6)-CH_3	$C_{28}H_{31}FN_4$	220	82.1	D-E	C, H, N, F	>2.5	-

[a] Based on immediate precursor, after recrystallization. Generally no attempts made to optimize yields. [b] Key: A = 2-propanol; B = methanol; C = 4-methyl-2-pentanone; D = acetone; E = diisopropyl ether. [c] See footnote *c* in Table I. [d] Prepared from **45** via catalytic nitro reduction. [e] Prepared via hydrogen peroxidation of **47**. [f] Confidence limits. [g] See footnote *q* in Table I. [h] See footnote *b* in Table I. [i] See footnote *c* in Table I.

water, and extracted twice with toluene. The combined organic layers were dried ($MgSO_4$), filtered, and evaporated. The residue was acidified with hydrogen chloride and crystallized from methanol to afford **8**: 1 g (18.3%); mp 300 °C. Anal. ($C_{25}H_{32}FN_5O \cdot 3HCl$) C, H, N, Cl.

4-[[1-[(4-Fluorophenyl)methyl]-1*H*-benzimidazol-2-yl]amino]-1-piperidineacetonitrile (9). A suspension of **1** (24.3 g, 0.05 mol), chloroacetonitrile (3.8 g, 0.05 mol), sodium carbonate

Table III. Intravenous Histamine Lethality Test in Guinea Pigs[3]

compd	ED_{50} values, mg/kg h after administrn				
	3	8	24	48	96
4	0.04	0.07	0.09	0.30	2.15
51	0.33	0.17	0.07	0.04	0.19
55	0.19	0.08	0.06	0.12	0.27
azatadine	0.014 (0.011–0.018)[a]	0.06 (0.02–0.17)[a]	1.36 (1.04–1.78)[a]	>2.5	
cyproheptadine	0.08 (0.04–0.16)[a]	0.88 (0.44–1.43)[a]	>2.5		
oxatomide	0.20 (0.010–0.31)[a]	1.25 (0.44–1.43)[a]	>5		

[a] Confidence limits.

Table IV. Protection from Compound 48/80 Lethality. Inhibition of Histamine- and Serotonin-Skin Reactions, and Mydriatic Activity in Rat: Comparison of Effective Dose of Astemizole and Reference Compounds

compd	ED_{50} values, mg/kg						
	compd 48/80 lethality:	histamine–skin reaction		serotonin–skin reactions		mydriatic act.	
	oral 2 h	oral 2 h	sc 2 h	oral 2 h	sc 2 h	oral 2 h	ip
2	2.5		0.04		≥0.63		>40
4	0.63		0.08		>0.63		>40
astemizole (51)	0.11 (0.08–0.16)[a]	0.13 (0.08–0.19)	0.15	14.2 (8.3–24.5)	>2.5	>160	>40
55	0.10		0.08		≥0.63		>40
azatadine	0.48 (0.32–0.70)	0.77 (0.48–1.25)		18.8 (11.6–30.3)		5.39 (3.60–8.06)	
cyproheptadine	1.13 (0.86–1.48)	0.89 (0.46–1.69)		2.35 (1.45–3.79)		9.36 (6.91–12.7)	
oxatomide	5.37 (4.34–6.65)	9.36 (6.25–14.0)		32.6 (21.6–48.8)		>160.0	
pyrilamine	56.6 (46.0–69.8)	>40.0		>40.0		56.5 (41.7–76.6)	

[a] 95% confidence limits.

(15.9 g, 0.15 mol), and potassium iodide (0.1 g) in dimethylformamide (150 mL) was stirred at 60 °C for 2 h. The cooled reaction mixture was poured into water and extracted twice with toluene. The combined organic fractions were dried ($MgSO_4$), filtered, and evaporated in vacuo. The residue was crystallized from a 4-methyl-2-pentanone–diisopropyl ether mixture to afford **9**: 10 g (55%); mp 178.7 °C. Anal. ($C_{21}H_{22}FN_5$) C, H, N.

***N*-[1-(2-Aminoethyl)-4-piperidinyl]-1-[(4-fluorophenyl)methyl]-1*H*-benzimidazol-2-amine Trihydrochloride (10).** A solution of **9** (9 g, 0.025 mol) in methanol (250 mL) saturated with ammonia was hydrogenated over RaNi (3 g) at normal pressure and room temperature. After uptake of 2 equiv of hydrogen, the catalyst was filtered off and the filtrate was evaporated. Crystallization of the residue from acetone–methanol acidified with HCl afforded **10**: 11g (92%); mp 292.9 °C. Anal. ($C_{21}H_{26}FN_5 \cdot 3HCl$) C, H, N, Cl, H_2O.

***N*-[1-[2-(Dimethylamino)ethyl]-4-piperidinyl]-1-[(4-fluorophenyl)methyl]-1*H*-benzimidazol-2-amine (11).** A solution of **10** (3.5 g, 0.009 mol) and paraformaldehyde (1 g) in methanol (150 mL) was hydrogenated over Pd/C (10%, 2 g). The catalyst was poisened by adding 1 mL of a 4% solution of thiophene in methanol (v/v). After uptake of 2 equiv of hydrogen, the catalyst was filtered off and the solvent was evaporated in vacuo. The residue was treated with water (100 mL) and extracted with chloroform (200 mL). The organic layer was separated, dried ($MgSO_4$), filtered, and evaporated. Crystallization of the residue from a mixture of acetone and diisopropyl ether yielded **11**: 1.5 g (42%); mp 166.1 °C. Anal. ($C_{23}H_{30}FN_5$) C, H, N, F.

***N*-[2-[4-[[1-[(4-Fluorophenyl)methyl]-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]-*N*-methylurea Hemihydrate (14).** A solution of **10** (4.77 g, 0.01 mol) in methanol (100 mL) was basified with ammonia. After evaporation in vacuo, methyl isocyanate (0.6 g, 0.01 mol) in tetrahydrofuran (200 mL) was added and the solution was stirred overnight at room temperature. The precipitate was collected and dried in vacuo to furnish **14**: 3 g (70.7%); mp 231.4 °C. Anal. ($C_{23}H_{29}FN_6O \cdot {}^1/_2H_2O$) C, H, N, F, H_2O.

***N*-[2-[4-[[1-[(4-Fluorophenyl)methyl]-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]-4-methoxy-*N*-(4-methoxybenzoyl)benzamide Dihydrochloride Dihydrate (15).** A solution of 4-methoxybenzoyl chloride (1.7 g, 0.01 mol) in dichloromethane (50 mL) was added dropwise to a suspension of **10** (free base) (3.8 g, 0.01 mol) and triethylamine (1 g, 0.01 mol) in dichloromethane (100 mL) at room temperature. After stirring for 24 h, the reaction mixture was poured into water and the organic layer was separated, dried ($MgSO_4$), filtered, and evaporated in vacuo. The residue was purified on silica gel (eluant $CHCl_3$–CH_3OH 98:2 (v/v)). The product was collected and crystallized from 2-propanol acidified with HCl to yield **15**: 1 g (13.4%); mp 161.5 °C. Anal. ($C_{37}H_{38}FN_5O_4 \cdot 2HCl \cdot 2H_2O$) C, H, N, Cl, F, H_2O.

1-[(4-Fluorophenyl)methyl]-*N*-[1-[3-[(4-methoxyphenyl)thio]propyl]-4-piperidinyl]-1*H*-benzimidazol-2-amine (22). A suspension of 1-[(3-chloropropyl)thio]-4-methoxybenzene (6.5 g, 0.03 mol),[21] **1** (14.7 g, 0.03 mol), and sodium carbonate (10.6 g, 0.1 mol) in dimethylformamide (200 mL) was stirred overnight at 70 °C. The usual workup furnished a residue, which was purified on silica gel (eluent $CHCl_3$–CH_3OH 98:2 (v/v)). The product was collected and crystallized from acetone–diisopropyl ether to afford **22**: 10 g (66%); mp 114.5 °C. Anal. ($C_{29}H_{33}FN_4OS$) C, H, N.

1-[(4-Fluorophenyl)methyl]-*N*-[1-[3-[(4-methoxyphenyl)sulfonyl]propyl]-4-piperidinyl]-1*H*-benzimidazol-2-amine Ethanedioate (1:2) 23. Hydrogen peroxide (30%; 2.2 mL, 0.02 mol) was added slowly to a solution of **22** (3.7 g, 0.007 mol) in acetic acid (20 mL). The solution was stirred and refluxed for 1 h. The cooled reaction mixture was basified with sodium hydroxide (50%) and extracted twice with chloroform. The combined organic layers were dried ($MgSO_4$), filtered, and evaporated. The residue was purified on silica gel, and the oxalate salt was crystallized from a mixture of methanol and 2-propanol to yield **23**: 0.8 g (16%); mp 213.1 °C. Anal. ($C_{29}H_{33}FN_4O_3S \cdot 2(COOH)_2$) C, H, N, F.

1-[4-[3-[4-[[1-[(4-Fluorophenyl)methyl]-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]-2-hydroxypropoxy]phenyl]ethanone (28). A solution of 1-[4-(oxiranylmethoxy)phenyl]ethanone (2.9 g, 0.015 mol),[22] **1** (4.9 g, 0.1 mol), and sodium carbonate (2.1 g, 0.02 mol) in methanol (50 mL) and benzene (100 mL) was stirred and refluxed for 24 h. After filtration and concentration in vacuo the product was crystallized from 2-propanol to afford **28**: 1.8 g (35%); mp 174.7 °C. Anal. ($C_{30}H_{33}FN_4O_3$) C, H, N, F.

1-[(4-Fluorophenyl)methyl]-*N*-[1-[2-(4-pyridinyl)ethyl]-4-piperidinyl]-1*H*-benzimidazol-2-amine (39). A solution of 4-vinylpyridine (1.5 g, 0.015 mol) and **1** (free base) (3.2 g, 0.010 mol) in butanol (150 mL) was stirred and refluxed overnight. After concentration in vacuo, the product was chromatographed on silica (eluant $CHCl_3$–CH_3OH 97:3 (v/v)) and crystallized from 4-methyl-2-pentanone to afford **39**: 1.5 g (35%); mp 158.2 °C. Anal. ($C_{26}H_{28}FN_5$) C, H, N, F.

(21) Bird, R.; Stirling, C. J. M. *J. Chem. Soc. B* **1968**, 111.
(22) Schubz, H. *Pharmazie* **1968**, *23*, 240.

1-[(4-Fluorophenyl)methyl]-*N*-[1-[2-(4-methoxyphenyl)-ethyl]-4-piperidinyl]-1*H*-benzimidazol-2-amine (51). A suspension of (4-methoxyphenyl)ethanol methanesulfonate ester (2.3 g, 0.01 mol),[23] 1 (4.9 g, 0.01 mol), and sodium carbonate (3.2 g, 0.03 mol) in dimethylformamide (100 mL) was stirred overnight at 70 °C. The cooled reaction mixture was poured into water and extracted twice with toluene. The organic layers were dried ($MgSO_4$), filtered, and evaporated. Chromatographic purification and crystallization from diisopropyl ether furnished **51**: 2.2 g (48%); mp 171.4 °C. Anal. ($C_{28}H_{31}FN_4O$) C, H, N, F.

1-[(4-Fluorophenyl)methyl]-*N*-[1-[2-[4-(phenylmethoxy)phenyl]ethyl]-4-piperidinyl]-1*H*-benzimidazol-2-amine (54). A suspension of 2-[4-(phenylmethoxy)phenyl]ethyl methanesulfonate (ester) (13.5 g, 0.044 mol), 1 (19.5 g, 0.040 mol), and sodium carbonate (1.7 g, 0.12 mol) in dimethylformamide (500 mL) was stirred at 70 °C for 20 h. The usual workup afforded the crude residue, which was crystallized from a mixture of acetone and diisopropyl ether to yield **54**: 10 g (46.7%); mp 155.4 °C. Anal. ($C_{34}H_{35}FN_4O$) C, H, N, F.

4-[2-[4-[[1-[(4-Fluorophenyl)methyl]-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]phenol Hemihydrate (55). (i) A solution of **51** (9.2 g, 0.02 mol) in 48% hydrobromic acid (300 mL) was stirred and refluxed for 20 h. The solvent was evaporated in vacuo, and the residue was basified with sodium hydroxide (50%) in ice water. After extraction with chloroform, the organic layer was dried ($MgSO_4$), filtered, and extracted. The pure residue was triturated with diisopropyl ether, and the precipitate was collected and dried in vacuo to afford **55**: 8.5 g (93%); mp 110.4 °C.

(ii) A solution of **54** (7.5 g, 0.014 mol) in methanol (150 mL) was debenzylated over Pd/C (10%, 2 g). After uptake of 1 equiv of hydrogen, the catalyst was filtered off, and the filtrate was evaporated. The residue was triturated in diisopropyl ether to yield pure **55**: 5.5 g (88.5%); mp 111.4 °C. Anal. ($C_{27}H_{29}FN_4O$) C, H, N, H_2O.

Methyl 2-[4-[2-[4-[[1-[(4-Fluorophenyl)methyl]-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]phenoxy]acetate (57). A suspension of methyl monochloroacetate (3.26 g, 0.03 mol), **55** (13.5 g, 0.03 mol), and potassium carbonate (4.2 g, 0.03 mol) in acetone (200 mL) was stirred and refluxed overnight. The reaction mixture was filtered and evaporated in vacuo, and the residue was purified on silica (eluant $CHCl_3$–CH_3OH 98:2 (v/v)). The product was collected and crystallized from a mixture of acetone and diisopropyl ether to afford **57**: 5 g (32%); mp 109.8 °C. Anal. ($C_{30}H_{33}FN_4O_3$) C, H, N, F.

2-[4-[2-[4-[[1-[(4-Fluorophenyl)methyl]-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]phenoxy]acetamide (59). A solution of **57** (3.5 g, 0.007 mol) in methanol (50 mL) and aqueous ammonia (100 mL) was stirred at room temperature for 4 h. Following concentration, the residue was chromatographed on silica (eluant $CHCl_3$–CH_3OH 95:5 (v/v)) to afford the pure product, which was crystallized from 2-propanol to yield **59**: 1 g (29.6%); mp 180.4 °C. Anal. ($C_{29}H_{32}FN_5O_2$) C, H, N, F.

1-[2-[4-[2-[4-[[1-[(4-Fluorophenyl)methyl]-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]phenoxy]acetyl]-piperidine Dihydrochloride (61). A suspension of **55** (6.24 g, 0.01 mol), *N*-(chloroacetyl)piperidine (1.6 g, 0.01 mol),[24] and potassium carbonate (4.2 g, 0.03 mol) in acetone (150 mL) was stirred and refluxed overnight. The reaction mixture was filtered and evaporated. The residue was purified on silica (eluant $CHCl_3$–CH_3OH 95:5 (v/v)). The product was collected and crystallized from 2-propanol acidified with hydrogen chloride to afford **61**: 2.8 g (43.5%); mp 247 °C. Anal. ($C_{34}H_{40}FN_5O_2$·2HCl) C, H, N, Cl.

4-[2-[4-[[1-[(4-Fluorophenyl)methyl]-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]phenyl 4-Methoxybenzoate (64). Acylation of **55** (4.5 g, 0.01 mol) with 4-methoxybenzoyl chloride (1.7 g, 0.01 mol) in dichloromethane as described for **4** yielded, after the usual workup, a crude residue of **64**. Chromatographic purification (eluant $CHCl_3$–CH_3OH 98:2 (v/v)), followed by crystallization of the product from a mixture of acetone and diisopropyl ether afforded **64**: 1 g (17%); mp 157.1 °C. Anal. ($C_{35}H_{35}FN_4O_3$) C, H, N, F.

4-[2-[4-[[1-[(4-Fluorophenyl)methyl]-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]phenyl Phenylmethyl Carbonate (67). A solution of benzyl chloroformate (1.7 g, 0.01 mol) in dichloromethane (50 mL) was added dropwise to a solution of **55** (4.5 g, 0.01 mol) and triethylamine (1 g, 0.01 mol) in dichloromethane (100 mL) at room temperature. The reaction mixture was refluxed for 1 h and stirred overnight at room temperature. The mixture was poured into water, and the organic layer was separated and washed twice with water. The organic layer was dried ($MgSO_4$) and evaporated and the residue chromatographed on silica (eluant $CHCl_3$–CH_3OH 95:5 (v/v)). The product was collected and crystallized from 2-propanol to yield **67**: 2.5 g (43%); mp 147.8 °C. Anal. ($C_{35}H_{35}FN_4O_3$) C, H.

4-[2-[4-[[1-[(4-Fluorophenyl)methyl]-1*H*-benzimidazol-2-yl]amino]-1-piperidinyl]ethyl]phenyl Butylcarbamate (68). A solution of *n*-butyl isocyanate (1 g, 0.01 mol) and **55** (4.5 g, 0.01 mol) in tetrahydrofuran (150 mL) was stirred and refluxed for 20 h. The solvent was removed in vacuo, and the residue was purified on silica (eluant $CHCl_3$–CH_3OH 98:2 (v/v)). Crystallization of the purified product from a mixture of acetone and diisopropyl ether furnished **68**: 1 g (18%); mp 142.5 °C. Anal. ($C_{32}H_{38}FN_5O_2$) C, H, N, F.

Ethyl 4-[(5-Fluoro-1*H*-benzimidazol-2-yl)amino]-1-piperidinecarboxylate (81; R = F). A solution of **79** (42.2 g, 0.2 mol) and **80** (R = F, 25.2 g, 0.2 mol) in methanol (300 mL) was stirred overnight at room temperature to afford quantitatively ethyl 4-[[[(2-amino-4-fluorophenyl)amino]thioxomethyl]-amino]-1-piperidinecarboxylate. Cyclodesulfurization[1] of the thiourea, followed by crystallization of the product from a mixture of tetrahydrofuran and diisopropyl ether, afforded **81** (R = F): 34.5 g (56.3%); mp 227.5 °C. Anal. ($C_{15}H_{19}FN_4O_2$) C, H, N, F.

Ethyl 4-[[5-Chloro-1-[(4-fluorophenyl)methyl]-1*H*-benzimidazol-2-yl]amino]-1-piperidinecarboxylate (82; R = Cl). A solution of **78** (R = Cl; 35 g, 0.125 mol) and **79** (23.6 g, 0.125 mol)[1] in methanol (500 mL) was stirred overnight at room temperature. The reaction was completed within 24 h (TLC), yielding ethyl 4-[[[[5-chloro-2-[[(4-fluorophenyl)methyl]amino]phenyl]-amino]thioxomethyl]amino]-1-piperidinecarboxylate. This thiourea was cyclodesulfurized, without further purification, as already described[1] to afford a crude residue of **82** (R = Cl). Crystallization from a mixture of 4-methyl-2-pentanone and diisopropyl ether gave an analytical sample: overall yield 46.5%; mp 215.8 °C. Anal. ($C_{22}H_{24}ClFN_4O_2$) C, H, N, Cl, F.

Ethyl 4-[[5(6)-Fluoro-1-[(4-fluorophenyl)methyl]-1*H*-benzimidazol-2-yl]amino]-1-piperidinecarboxylate (82; R = F; 83, R = F). A suspension of **81** (R = F, 15.3 g, 0.05 mol), 4-fluorobenzyl chloride (9 g, 0.06 mol), sodium carbonate (5.3 g, 0.05 mol), and potassium iodide (0.2 g) in dimethylformamide (150 mL) was stirred overnight at 70 °C. After the usual workup, the crude residue was crystallized from a mixture of acetone and diisopropyl ether to yield a 1:1 mixture (NMR) of **82** (R = F) and **83** (R = F): 13.4 g (62.1%); mp 182.5 °C. Anal. ($C_{22}H_{24}F_2N_4O_2$) C, H, N, F.

5-Chloro-1-[(4-fluorophenyl)methyl]-*N*-[1-(2-phenylethyl)-4-piperidinyl]-1*H*-benzimidazol-2-amine (84; R = Cl). (i) Deprotection of **82** (R = Cl) with 48% aqueous HBr afforded 5-chloro-1-[(4-fluorophenyl)methyl]-*N*-(4-piperidinyl)-1*H*-benzimidazol-2-amine dihydrobromide: 95%; mp 260 °C.

(ii) Coupling of the dihydrobromide (4 g, 0.009 mol) and phenylethyl bromide (3 g, 0.015 mol) in dimethylformamide yielded, after the usual workup, 4.5 g of the crude product. Chromatographic purification on silica (eluant $CHCl_3$–CH_3OH 97.5:2.5 (v/v)) followed by crystallization from a mixture of acetone and diisopropyl ether yielded an analytical sample of **84** (R = Cl): 1.3 g (30.2%); mp 168.3 °C. Anal. ($C_{27}H_{28}ClFN_4$) C, H, N, Cl, F.

5-Fluoro-1-[(4-fluorophenyl)methyl]-*N*-[(2-phenylethyl)-4-piperidinyl]-1*H*-benzimidazol-2-amine Monohydrate (85; R = F) and the 6-Fluoro Isomer (86; R = F). (i) Deprotection of the 5(6)-fluoro mixture **82** (R = F) and **83** (R = F) as already described[1] yielded a mixture of 5(6)-fluoro-1-[(4-fluorophenyl)methyl]-*N*-(4-piperidinyl)-1*H*-benzimidazol-2-amine dihydrobromide: 89%; mp >260 °C. Anal. ($C_{19}H_{20}F_2N_4$·2HBr) Br.

(23) Beard, C. C.; Eduards, J. A.; Fried, J. H. American Patent U.S. 3 929 824, 1976; *Chem. Abstr.* **1976**, *84*, 135653*v*.

(24) Guandini, A.; Schenone, P.; Minardi, G. *Farm. Ed. Sci.* **1963**, *18*, 828.

(ii) A suspension of the dihydrobromide salt (6 g, 0.012 mol), phenylethyl bromide (2.4 g, 0.013 mol), and sodium carbonate (3.2 g, 0.03 mol) in 4-methyl-2-pentanone (250 mL) was refluxed, and water was continuously removed with the aid of a Dean–Stark trap. After the usual workup, the residue was purified on silica (eluant $CHCl_3$–CH_3OH 97:3 (v/v)). The pure isomers were separated via HPLC (eluant ethyl acetate–methanol 93:7 (v/v)). The compound with the highest R_f value (TLC) was identified as the 5-isomer **85** (R = F) by NMR analysis. Trituration of **85** with diisopropyl ether afforded an analytical sample: 1 g (17.5%); mp 178.1 °C. Anal. ($C_{27}H_{28}F_2N_4 \cdot H_2O$) C, H, N, F, H_2O.

The other component was characterized as the 6-fluoro isomer **86** (R = F) by NMR analysis; 1.2 g (21%); mp 188.8 °C. Anal. ($C_{27}H_{28}F_2N_4$) C, H, N, F.

Pharmacological Methods. In Vitro Screening. A. Inhibition of Histamine- (H_1-) Induced Contraction of Guinea Pig Ileum: determined as previously described.[1,25]

B. Inhibition of Histamine- (H_2-) Induced Increase in Heart Rate of Guinea Pig Atrium. Spontaneous beating right atria of guinea pigs (400–500 g, fasted overnight) were suspended with an optimal preload (i.e., the preload at which the isometric force development is maximal) in a 100-mL Krebs–Henseleit bath, containing 0.026 mM CaEDTA, gassed with a mixture of 95% O_2 and 5% CO_2 (37.5 °C). Both contractile force and heart rate were measured (isometrical force transducer Grass FT O3C, JSI amplifier, cardiotachometer JSI, Honeywell 540 XYY′ pen-recorder). A dose–response curve was made by constant infusion of histamine (concentration increase of 4.9×10^{-6} M for 7 min) into the organ bath before, and 30 min after, the addition of the antagonist.

The gradual agonist-induced increase in heart rate and contractile force was recorded continuously. Direct chronotropic and inotropic effects were observed during the incubation period. A change of slope of the agonist–frequency curve was taken as a measure of drug effect.[8]

C. **Inhibition of Histamine- (H_2) Induced Gastric Acid Secretion of the Rat Stomach.** Sucking male Wistar rats (20 days of age, weighing about 40 g) were anaesthetized by ip injection of 3 mg of pentobarbital. The stomach was taken out after ligation of the esophagus. The duodenum and the fundic part were cannulated for in flow (duodenum) and out flow (fundus) of buffer-free Krebs–Henseleit solution (without $NaHCO_3$ and KH_2PO_4) with a perfusion rate of 1 mL/min.[26] The stomach was suspended in a 10 mL of Krebs–Henseleit bath, gassed with a mixture of 95% O_2 and 5% CO_2 (37.5 °C). The pH of the outflowing perfusate was continuously monitored (Philips PW 9409) and expressed as concentration of H^+ ions (Dual acid gastric secretion calculator; JSI, HP XY 7035 B). With pyrilamine (3.5×10^{-7} M) present in the bathing solution, a single dose of histamine (5.4×10^{-5} M) was added to the bath. Ten minutes later the antagonist was added for a period of 30 min. Inhibition of histamine-stimulated acid secretion was scored qualitatively.[8]

In Vivo Screening. A. Protection of Rats from Compound 48/80 Induced Lethality: determined as described previously.[2-4] Briefly, test compounds or solvents were given subcutaneously or orally to inbred Wistar rats (230–270 g) at various time intervals (usually 1 and 2 h, respectively) before a normally lethal intravenous injection of compound 48/80 (0.5 mg/kg) was administered. Protective activity was defined as survival of the animal for 4 h after the challenge. Drug effects were expressed as estimated ED_{50} values, i.e. the dose where 50% of the animals survive the challenge. Calculated ED_{50} values with confidence limits, according to Finney,[27] were obtained on the basis of test results on five animals for each of at least three doses from the geometrical series 0.0025, 0.005, 0.01, ..., 10.0, 20.0, 40.0 mg/kg. Estimated ED_{50} values were based on at least two animals per test dose.

B. Protection of Guinea Pigs from Histamine-Induced Lethality. The 50% protective dose (PD_{50}) values against a lethal intravenous dose of histamine were determined as previously described.[5] Male albino guinea pigs (280–360 g) were challenged with an intravenous injection of 1.25 mg/kg of histamine dihydrochloride solution. As all control animals died within 5 min, survival after 1 h was considered to be a safe criterion of protection from histamine-induced death. PD_{50} values with confidence limits were computed according to Finney.[27] To study the duration of action, 2-fold increments of the test substance were administered orally 3, 24, 48, and 96 h prior to an intravenous histamine challenge. Four to six guinea pigs per dose and time point were used for each of at least three doses from the geometrical series 0.0025, 0.005, 0.01, ..., 2.5, 5.0 mg/kg. Estimated PD_{50} values were based on at least two animals per test dose.

C. **Histamine- and Serotonin-Induced Skin Reactions in Rats.** Two hours after oral administration of test compounds or solvent, four intradermal injections, two of 50 μL of histamine dihydrochloride solution (1 mg/mL in saline) and two of 50 μL of serotonin solution (2 μg/mL in saline), were given into the clipped back of a rat. These were immediately followed by an intravenous injection of 0.5 mL of a 0.5% trypan blue solution. Thirty minutes later, the bluing of the cutaneous reactions was scored as previously described.[6]

D. Peripheral and Central Effects Not Related to Histamine Antagonism. Astemizole (**51**), or solvent, was administered orally 2 h before testing. In rats, mydriatic activity, antagonism of noradrenaline-induced lethality, of apomorphine-induced agitation and stereotypy and of tryptamine-induced tremors were investigated as described previously.[7] Palpebral ptosis and catalepsy-inducing properties,[9] inhibition of food intake,[10] inhibition of intracranial self-stimulation,[11] and locomotor activity[12] were also studied according to standard procedures. In dogs, antagonism of apomorphine-induced emesis was performed as described previously.[13]

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Registry No. 1, 75970-99-9; 1·2HBr, 75970-64-8; **2**, 73735-88-3; **3**, 73735-89-4; **4**, 90519-49-6; 4·HBr, 73735-86-1; 4·2HCl, 75971-22-1; **5**, 75971-24-3; 5·2HCl, 73736-56-8; 6·2HCl, 73736-53-5; **7**, 73736-54-6; **8**, 75971-23-2; 8·3HCl, 73736-55-7; **9**, 73735-20-3; **10**, 75971-26-5; 10·3HCl, 73736-67-1; **11**, 73736-74-0; **12**, 73736-75-1; **13**, 73736-01-3; 14, 73736-72-8; **15**, 75971-27-6; 15·2HCl, 73736-73-9; **16**, 73734-59-5; **17**, 73735-31-6; **18**, 75971-00-5; **19**, 75971-04-9; **20**, 73735-05-4; **21**, 73734-79-9; **22**, 73735-11-2; **23**, 73756-00-0; **23**·$2C_2H_2O_4$, 75979-03-2; **24**, 98088-81-4; 24·2HCl, 73735-98-5; **25**, 98088-82-5; **26**, 75971-02-7; **27**, 75971-08-3; **28**, 73735-82-7; **29**, 75971-09-4; **30**, 73734-74-4; **31**, 73735-13-4; **32**, 73734-71-1; **33**, 73735-90-7; **34**, 73734-72-2; **34**·2HNO_3, 73734-73-3; **35**, 73734-75-5; **36**, 73735-65-6; **37**, 73734-99-3; **38**, 73735-69-0; **39**, 73735-71-4; **40**, 73735-67-8; **41**, 98088-83-6; 41·2HCl, 73734-98-2; **42**, 75971-12-9; **43**, 98088-84-7; 43·2HCl, 73734-43-7; **44**, 98088-85-8; 44·2HCl, 73734-86-8; **45**, 73734-53-9; **46**, 73736-49-9; **47**, 73735-14-5; **48**, 73735-15-6; **49**, 73735-41-8; **50**, 75971-19-6; 50·2HCl, 73735-40-7; **51**, 68844-77-9; **52**, 75971-20-9; 52·2HCl, 73736-51-3; **53**, 73735-39-4; **54**, 73735-55-4; **55**, 73736-50-2; **56**, 75971-21-0; 56·2HCl, 73736-52-4; **57**, 73736-63-7; **58**, 73736-62-6; **59**, 75971-31-2; **60**, 75971-30-1; **61**, 98088-86-9; 61·2HCl, 73736-64-8; **62**, 75971-25-4; 62·2HCl, 73736-61-5; **63**, 73736-57-9; **64**, 73736-58-0; **65**, 73736-65-9; **66**, 73736-59-1; **67**, 73736-60-4; **68**, 73736-66-0; **69**, 98088-87-0; 69·2HCl, 73755-99-4; **70**, 73735-62-3; **71**, 98088-88-1; 71·2HCl, 73735-59-8; **72**, 73735-37-2; **73**, 73735-38-3; **74**, 98088-89-2; 74·2HCl, 73735-63-4; **75**, 98088-90-5; 75·2HCl, 73735-44-1; **76**, 140-75-0; **77** (R = Cl), 89-61-2; **78** (R = Cl), 75971-32-3; **79**, 73733-70-7; **80** (R = F), 367-31-7; 81 (R = F), 73734-00-6; **82** (R = Cl), 73755-75-6; **82** (R = F), 75970-37-5; **82** (R = CH_3), 98088-91-6; **82** (R = H), 84501-68-8; **82** (R = H,1-debenzyl deriv.), 73734-07-3; **82** (L = H,R = Cl)·2HBr, 73734-22-2; **82** (L = H,R = F)·2HBr, 98088-93-8; **83** (R = F), 75970-38-6; **83** (R = CH_3), 98088-92-7; **83** (L = H,R = F)·2HBR, 98088-94-9; **84**, 73734-47-1; **85**, 73735-29-2; **86**, 73735-28-1; **87** (5-CH_3), 75970-78-4; **87** (6-CH_3), 75970-79-5; 4-$FC_6H_4CH_2Cl$, 352-11-4; 4-$CH_3OC_6H_4COCl$, 100-07-2; $ClCH_2CN$, 107-14-2; CH_3NCO, 624-83-9; 4-$CH_3OC_6H_4S(CH_2)_3Cl$, 19433-01-3; 4-$CH_3OC_6H_4(CH_2)_2OSO_2CH_3$, 73735-36-1; 4-$(C_6H_5CH_2O)C_6H_4$-

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$(CH_2)_2OSO_2CH_3$, 61439-60-9; n-C_4H_9NCO, 111-36-4; cyclohexanone, 108-94-1; ethylene oxide, 75-21-8; 1-[4-(oxiranylmethoxy)phenyl]ethanone, 19152-55-7; 4-vinylpyridine, 100-43-6; *N*-(chloroacetyl)piperidine, 1440-60-4; ethyl 4-[[[(2-amino-4-fluorophenyl)amino]thioxomethyl]amino]-1-piperidinecarboxylate, 73733-85-4; ethyl 4-[[[[5-chloro-2-[[(4-fluorophenyl)methyl]amino]phenyl]amino]thioxomethyl]amino]-1-piperidinecarboxylate, 73733-86-5.

New Antihistaminic N-Heterocyclic 4-Piperidinamines. 3. Synthesis and Antihistaminic Activity of *N*-(4-Piperidinyl)-3*H*-imidazo[4,5-*b*]pyridin-2-amines

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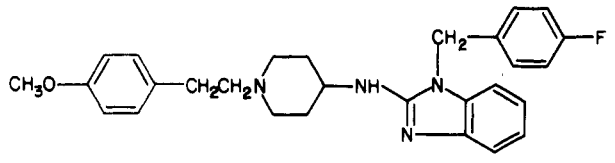
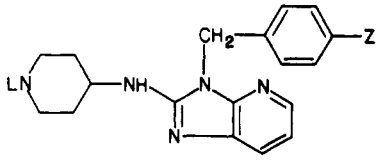
To study the bioisosteric replacement of a 2-pyridyl ring for a phenyl nucleus in astemizole, a series of *N*-(4-piperidinyl)-3*H*-imidazo[4,5-*b*]pyridin-2-amines was synthesized and evaluated. The title compounds were obtained starting from either **8a** or **8b** by four synthetic methods. The in vivo antihistamine activity was evaluated by the compound 48/80-induced lethality test in rats and the histamine-induced lethality test in guinea pigs after oral and/or subcutaneous administration. Compound **37**, the isostere of astemizole, showed the most potent antihistaminic properties in the rat. However, astemizole is superior to **37** as to duration of action and total potency.

Astemizole, a prototype of a new series of *N*-(4-piperidinyl)-1*H*-benzimidazol-2-amines, is a potent, long-lasting, and selective in vivo antihistamine, not affecting the central nervous system in different animal species, after both oral and subcutaneous administration.[1-3]



astemizole



I, Z = H or F

Replacement of a phenyl nucleus by a 2-pyridyl ring in the structure of various classical H_1-antagonists considerably enhances antihistaminic activity.[4] A series of *N*-(4-piperidinyl)-3*H*-imidazo[4,5-*b*]pyridin-2-amines (I) was synthesized in order to evaluate this well-known bioisosteric replacement[5] in astemizole and related compounds.

Chemistry. In the synthetic approach to the *N*-(4-piperidinyl)-3*H*-imidazo[4,5-*b*]pyridin-2-amines, benzylamine **1** was allowed to react with 2-chloro-3-nitropyridine (**2**) to form **3a,b** (Scheme I). Catalytic reduction of the nitro function of **3a,b** quantitatively yielded **4a,b**, which were immediately coupled with isothiocyanate **5**[1] to yield **6a,b**. Cyclodesulfurization of **6a,b** with mercury oxide in tetrahydrofuran afforded **7a,b**.[1] Deprotection with 48% HBr at reflux gave the intermediates **8a,b** (Table I).

The test compounds **9–39** originated from **8a,b** by one of the following four methods:[1,2] alkylation with LX in dimethylformamide at 70–90 °C (method A); addition of vinylpyridines in butanol (method B); reductive amination of ketones or aldehydes (method C); oxirane cleavage in a benzene–methanol mixture (method D).

Results and Discussion

The in vivo, antihistamine activity was evaluated by the compound 48/80-induced lethality test in rats;[6] the results

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(2) Part 2: Janssens, F.; Torremans, J.; Janssen, M.; Stokbroekx, R. A.; Luyckx, M.; Janssen, P. A. J. *J. Med. Chem.*, second of three papers in this issue.
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