Articles

1-(2-Pyridinyl)piperazine Derivatives with Antianaphylactic, Antibronchospastic, and Mast Cell Stabilizing Activities

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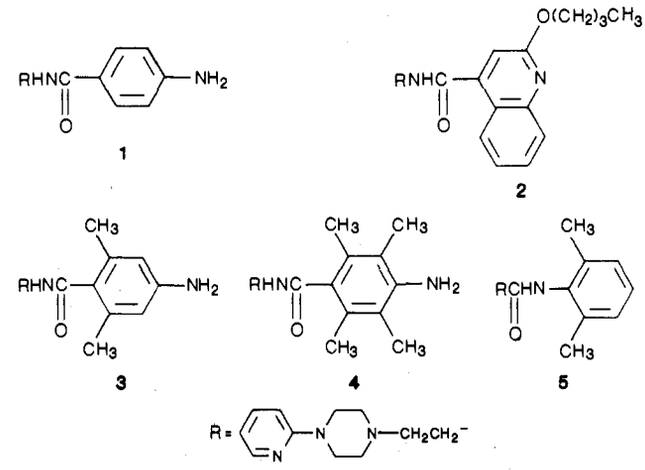
New 1-(2-pyridinyl)piperazine derivatives were synthesized and tested as inhibitors of the reaginic passive cutaneous anaphylaxis in the rat (PCA), of the histamine-induced bronchospasm in the guinea pig, and of the rat mesenteric mast cell degranulation induced by compound 48/80. On the basis of test results, a series of *N*-(substituted phenyl)-ω-[4-(2-pyridinyl)-1-piperazinyl]alkanamides was prepared. The nature of substituents at the anilide ring strongly influenced mast cell stabilizing activity, whereas it was less determining in the case of the other two tests. No clear correlation between the most common physicochemical parameters (π, σ, Vw volume) of substituents and activity could be detected. With regard to the position of substituents at the anilide ring, the rank order of potency, in the PCA and bronchoconstriction tests, was para > meta > ortho. Introduction of substituents in the 1-(2-pyridinyl)piperazinyl moiety of the *N*-(substituted phenyl)propanamide derivatives hardly affected activity, or the effect was deleterious. Some of the new compounds exhibited a simultaneous remarkable activity in all the three assays employed.

The synthesis of antiallergy compounds represents a vast area of activity for medicinal chemists. Beyond the class of "pure" mediator-release inhibitors, descending from disodium cromoglycate (DSCG), other substances have been developed showing antiallergy–antihistamine activity, e.g. ketotifen[1] [4,9-dihydro-4-(1-methyl-4-piperidinylidene)-10*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-10-one] and oxatomide[2] [1-[3-[4-(diphenylmethyl)-1-piperazinyl]propyl]-1,3-dihydro-2*H*-benzimidazol-2-one].

A good antianaphylactic effect and antagonism to histamine-induced bronchospasm have been reported for compound S 1688 (**1**) and its derivatives.[3] SAR studies for this series pointed out the importance of the *p*-amino group in the phenyl ring of the [4-(2-pyridinyl)-1-piperazinyl]ethyl moiety. Since compound **1** may be related to procainamide [4-amino-*N*-[2-(diethylamino)-ethyl]benzamide], we considered it interesting to prepare, and study for their potential antiallergy–antihistamine properties, new compounds having in their structure the [4-(2-pyridinyl)-1-piperazinyl]ethyl moiety linked to other moieties present in the structure of well-known local anaesthetic drugs.

We argued that compounds having "membrane-stabilizing" properties should be able to inhibit the release of allergic mediators or to inhibit the airway muscle contraction. Such properties have been reported for lidocaine [2-(diethylamino)-*N*-(2,6-dimethylphenyl)acetamide] which, at high concentrations in vitro, inhibits release of allergic mediators[4] and directly relaxes airway smooth muscle.[5] On these bases, we prepared compounds **2–5**.

Compounds **2** and **5** are related to dibucaine [2-butoxy-*N*-[2-(diethylamino)ethyl]-4-quinolinecarboxamide] and lidocaine, respectively; the preparation of compound **3** was suggested by the paper of D. K. Yung et al.,[6] who reported that the introduction of two methyl groups in the *o,o'*-position of procainamide retained the membrane-stabilizing effect of the parent compound. Compound **4** was prepared both as a continuation of our research on durene (1,2,4,5-tetramethylbenzene) derivatives[7] and on the basis of the observation that the 2,3,5,6-tetramethyl derivative of procainamide retains local anaesthetic activity.[8] Screening results for these compounds confirmed



in part our hypothesis, pointing at compound **5** as the most interesting substance.

Accordingly, we prepared a series of *N*-(substituted phenyl)-ω-[4-(2-pyridinyl)-1-piperazinyl]alkanamides (**8–49**; Table II). Furthermore, compounds **50–56** (Table III) were synthesized to broaden our knowledge about derivatives of 1-(2-pyridinyl)piperazine.

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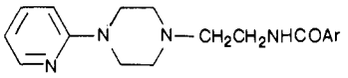
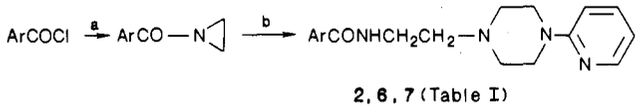
Table I. *N*-[2-[4-(2-Pyridinyl)-1-piperazinyl]ethyl]aroylamides



compd	Ar	method[a]	yield, %	recryst solvent[b]	mp, °C	formula	anal.
2	2-*n*-C_4H_9O-4-quinolyl	A	71[c]	E	146–147	$C_{25}H_{31}N_5O_2$	C, H, N
				W + A	207 dec	$C_{25}H_{31}N_5O_2 \cdot 2HCl \cdot {}^1/_2H_2O$	C, H, N, Cl, H_2O
3	2,6-$(CH_3)_2$-4-$NH_2C_6H_2$	B	52	M + A	266–271	$C_{20}H_{27}N_5O \cdot 3HCl \cdot H_2O$	C, H, N, Cl, H_2O
4	2,3,5,6-$(CH_3)_4$-4-NH_2C_6	B	76	I	170–172	$C_{22}H_{31}N_5O$	C, H, N
6	2,6-$(CH_3)_2$-4-$NO_2C_6H_2$	A	88[c,d]	E	176–177	$C_{20}H_{25}N_5O_3$	C, H, N
				E	262–266	$C_{20}H_{25}N_5O_3 \cdot 2HCl$	C, H, N, Cl
7	2,3,5,6-$(CH_3)_4$-4-NO_2C_6	A	68[c,e]	Et	166–167	$C_{22}H_{29}N_5O_3$	C, H, N
				M + D	>250	$C_{22}H_{29}N_5O_3 \cdot 2HCl$	C, H, N, Cl

[a] See the Experimental Section. [b] A = Me_2CO, D = Et_2O, E = EtOH, Et = EtOAc, I = *i*-PrOH, M = MeOH, W = H_2O. [c] The indicated yield refers to the last step: the nucleophilic opening of the aziridine ring. [d] The crude intermediate aroylaziridine (see ref 6) was obtained in 91% yield and used without purification. [e] The crude intermediate aroylaziridine was obtained in 90% yield and used without purification.

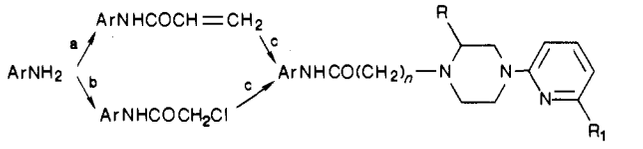
Scheme I[a]



2, 6, 7 (Table I)

[a] Key: a = aziridine; b = 1-(2-pyridinyl)piperazine.

Scheme II[a]



5, 8, 17, 19–24, 31–38, 40–42, 49 (Table II)

[a] Key: *n* = 1, 2; a = 2-propenoyl chloride; b = chloroacetyl chloride; c = appropriate 1-(2-pyridinyl)piperazine.

Chemistry

The synthesis of the tested compounds followed established procedures. Compounds **2**, **6**, and **7** were prepared by nucleophilic opening with 1-(2-pyridinyl)piperazine of the three-membered ring of the appropriate *N*-aroylaziridines, obtained by amidation of the corresponding aroyl chlorides (Scheme I, method A).

Most of the *N*-(substituted phenyl)-ω-[4-(2-pyridinyl)-1-piperazinyl]alkanamides (**5**, **9–11**, **13–17**, **19–24**, **31–38**, **40–42**, **49**) were synthesized by conjugated addition of 1-(2-pyridinyl)piperazines to *N*-(substituted phenyl)-2-propenamides (Scheme II, method C). The acetamide derivatives **8** and **12** were prepared by alkylation of 1-(2-pyridinyl)piperazine with *N*-(substituted phenyl)-2-chloroacetamides (Scheme II, method D).

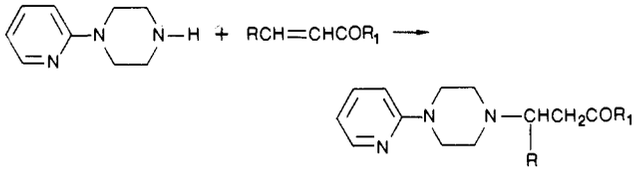
Compounds 3, **4**, **25–30**, **39**, and **43–48** were prepared, according to standard procedures (methods B and F–L), by modification of the substituents at the benzene ring, starting from the appropriate compounds obtained following the above indicated methods.

N-(4-Acetylphenyl)-3-[4-(5-bromo-2-pyridinyl)-1-piperazinyl]propanamide (**18**) was prepared by bromination at the pyridine ring of *N*-(4-acetylphenyl)-3-[4-(2-pyridinyl)-1-piperazinyl]propanamide (**17**) (method E).

Compounds **50–56** were prepared by conjugate addition of 1-(2-pyridinyl)piperazine to 2-propenoic or 2-butenoic acid derivatives (Scheme III).

Properties of compounds **2–56** are listed in Tables I–III. Although most of the required intermediates are described in the literature, some of the *N*-(substituted phenyl)-2-propenamides are new and were synthesized by acylation of the corresponding benzeneamines with 2-propenoyl chloride, following the general procedure reported in the Experimental Section for the *N*-(2,6-dimethylphenyl)-2-propenamide.

Scheme III



50–56 (Table III)

Pharmacological Results and Discussion

Compounds listed in Table I–III were first tested in a reaginic passive cutaneous anaphylaxis test in the rat (PCA)[9] and in a histamine-evoked bronchospasm in guinea pig (Konzett test).[10] For all tested compounds, indicative LD_{50}'s in the mouse were also calculated. Compounds exhibiting good levels of pharmacological activity and low toxicity were further investigated for mast cell stabilizing activity in a rat mesenteric mast cell degranulation, induced by compound 48/80, test.[11]

The results obtained for the newly synthesized compounds and for the standards (DSCG, oxatomide, ketotifen) are listed in Table IV. The anilide derivative **5** exhibited better results, in the rat PCA and Konzett tests, than the arylamide-type compounds **2–4**, **6**, and **7**. Also the toxicological (LD_{50}) data were more favorable for compound **5**.

Modifications in the structure of **5** were accordingly performed. The introduction of two additional methyl groups in the 3,5-position of the anilide ring (**11**) did not cause dramatic changes either in activity or in toxicity. On the contrary, a serious drop in activity was caused by shortening of the alkyl chain between the piperazine and the anilide moiety (**8**, **12**). According to the results of Regnier et al.,[3] no other structural change in the alkyl chain was attempted. Substitution of the *o*,*o*′-dimethyl groups in **5** by two chlorine atoms (**14**) and removal of one of the two *o*,*o*′-dimethyl substituents (**10**, **13**) gave substantially equiactive compounds. Variations in lipophilicity and in electronic and steric effects of the ortho substituent (**9**, **10**, **13**, **15**, **19**, **25**) afforded products with the same level of activity in the Konzett and PCA tests, with the only exception the 2-NO_2 derivative (**19**), which was inactive in the PCA test. At the same time a general reduction in toxicity was noticed, compound **15** being the least toxic after oral administration.

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Unsubstituted **9** and the above-mentioned ortho-substituted compounds, but **10** and **19**, were tested for their ability to counteract the mast cell degranulation induced by compound 48/80: none were active. The fact that the unsubstituted anilide **9** was more potent, in the PCA test after oral administration, than the ortho-substituted analogues, led us to investigate the effects of meta and para substitution. For this purpose the nitro (**20**, **21**), amino (**26**, **27**), acetyl (**16**, **17**), and methoxy (**32**, **33**) isomeric pairs were prepared. In the rat PCA and Konzett tests, the para-substituted isomers were generally more potent than the meta and the ortho derivatives, with the exception of the nitro derivatives, which showed a similar activity for the meta and the para isomer in both test systems. Furthermore, the introduction of substituents at the meta or para position of the anilide ring led in some cases to the appearance of inhibitory activity in the mast cell degranulation test (**20**, **27**), this activity being absent in the unsubstituted parent compound (**9**). Several other substituents were then introduced in the 4-position of the anilide ring of **9**. The relationships between the most common physicochemical parameters of the substituents (π, σ, Vw volume) and the pharmacological potencies in the rat PCA test (ip administration) and in the Konzett test were investigated, for meta- and para-monosubstituted derivatives, by multiple regression analysis. Poor significant correlation was found between the considered parameters and activity (maximum $R^2 < 0.35$).

Nevertheless, some observations may be made for this substitution pattern. In the rat PCA test (ip administration) a good number of compounds were active, the extreme ID_{50} values being 23 μmol/kg for the most active compound (**27**) and 194 μmol/kg for the least active one (**46**). It is interesting to note that derivatization of the 4-amino group (**43–48**) led to less potent or inactive compounds, the same trend being observable by increasing the bulkiness of the alkylthio derivatives (**35** vs. **36**). The po ID_{50} values for this test were usually higher than the ip values with the exception of derivatives **9** and **42** in which they were practically the same.

With regard to the inhibition of the histamine-induced bronchospasm, all the meta- and para-substituted derivatives showed potencies lying within 2 log units, the 4-acetyl (**17**) and the 4-amino (**27**) derivatives exhibiting the highest activity.

Higher selectivity emerged from the mast cell degranulation inhibition test, in which only compounds **20**, **27**, and **40** showed an activity level comparable to or better than that of DSCG. For the substituents present in these compounds (3-NO_2, 4-NH_2, 4-$COOC_2H_5$) no common unifying physicochemical characteristics may be found, except for the possibility of accepting H bonding, which on the other hand is present in most of the other substituents.

As far as the 1-(2-pyridinyl)piperazine moiety is concerned, the introduction of a methyl group in the piperazine ring (**23**, **28**) caused a lowering in activity, especially for **28**, which was less potent than the unsubstituted **27** both in the Konzett and in the mast cell degranulation tests. Similarly, the introduction of a methoxy group at position 6 of pyridine in **27**, to give **30**, resulted in lower activity in the Konzett test. The same modification of **19**, **21**, and **25**, to give **22**, **24**, and **29**, and the introduction of a bromine atom at position 5 of this ring in **17**, to give **18**, hardly affected activity. With regard to the derivatives listed in Table III, it may be noted that esters **51–53** and the amide **54** exhibited some activity in the rat PCA test, which was lost after introducing a methyl group in the alkyl chain (**55**, **56**). Compounds **50–56** showed a low activity level in the Konzett test.

The results of the present study show that a number of the synthesized compounds exhibit activity comparable to or better than the considered reference standards. The two most interesting compounds (**27**, **40**), exhibiting simultaneous presence of oral antianaphylactic (rat PCA test), antibronchospastic, and mast cell stabilizing activity, deserve further pharmacological investigations.

Experimental Section

Melting points were determined in open capillaries on a Büchi apparatus and are uncorrected. Elemental analyses are reported by symbols of element; results are within ±0.4% of the calculated values. ^1H NMR spectra, recorded on a Hitachi Perkin-Elmer R-24-A spectrometer at 60 MHz with Me_4Si as internal standard, and IR spectra, recorded on a Perkin-Elmer 297 spectrophotometer, were run on all compounds and support the structural assignments. Purity was checked by TLC, performed on silica gel glass plates (GF 254 Merck, 0.25 mm thick); all compounds gave a single spot. Column chromatography was performed on Merck silica gel 60. The hydrochlorides were prepared by conventional procedures and crystallized.

2-Butoxy-*N*-[2-[4-(2-pyridinyl)-1-piperazinyl]ethyl]-4-quinolinecarboxamide (2) (Method A). In a well-stirred, ice-cooled mixture of 0.6 N NaOH (200 mL), C_6H_6 (40 mL), and aziridine (1.72 g, 40 mmol), a solution of 2-butoxy-4-quinolinecarbonyl chloride (10.55 g, 40 mmol) in C_6H_6 (120 mL) was added dropwise, maintaining the temperature near 0–4 °C. After 1 h at 0–4 °C and 1 h at 15–20 °C, the organic phase was separated, and the aqueous layer was saturated with NaCl and extracted with C_6H_6. The combined organic solutions were dried and evaporated in vacuo to give 9.5 g (88%) of *N*-(2-butoxy-4-quinolinecarbonyl)aziridine as a thick oil, showing no detectable impurities in TLC (C_6H_6/petroleum ether, 1:1; $CHCl_3$/MeOH, 95:5) and a consistent NMR spectrum. A mixture of the above crude oil (9.46 g, 35 mmol) and 1-(2-pyridinyl)piperazine (5.74 g, 35 mmol) in C_6H_6 (70 mL) was refluxed for 2 h. After standing overnight, the mixture was cooled to 10 °C and the precipitate was collected by suction, dried, and crystallized. (See Table I.)

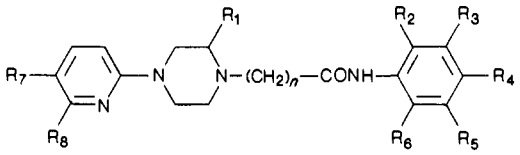
4-Amino-2,6-dimethyl-*N*-[2-[4-(2-pyridinyl)-1-piperazinyl]ethyl]benzamide Trihydrochloride Hydrate (3) (Method B). A suspension of 2,6-dimethyl-4-nitro-*N*-[2-[4-(2-pyridinyl)-1-piperazinyl]ethyl]benzamide (**6**; 7.67 g, 20 mmol) in MeOH (300 mL) was reduced with H_2 in the presence of 10% Pd/C catalyst (0.3 g) in a Parr apparatus with an initial pressure of 60 psi. After filtering, the solvent was evaporated and the residue purified by column chromatography using EtOAc as eluent. (See Table I.)

General Procedure for the Preparation of 3-[4-(2-Pyridinyl)-1-piperazinyl]alkanoyl Derivatives (Method C). A mixture of the appropriate 1-(2-pyridinyl)piperazine (10–12 mmol) and the appropriate 2-propenoic acid derivative (10 mmol) in toluene (10–20 mL) was refluxed until the reaction was completed (checked by TLC; 4–24 h). The crude reaction product was isolated by filtration or by solvent evaporation and rinsing of the residue with a suitable solvent. Depending upon the purity of the crude, crystallization or column chromatography followed by crystallization were employed to obtain pure compounds. (See Table II.)

***N*-(2,6-Dimethylphenyl)-2-[4-(2-pyridinyl)-1-piperazinyl]acetamide (8) (Method D).** A mixture of 1-(2-pyridinyl)piperazine (8.16 g, 50 mmol), $NaHCO_3$ (4.20 g, 50 mmol), and 2-chloro-*N*-(2,6-dimethylphenyl)acetamide (9.88 g, 50 mmol) in Me_2CO (125 mL) was stirred under reflux for 5 h. After cooling, the inorganic salts were collected and washed with Me_2CO. Mother liquor and washings were combined and evaporated in vacuo. The residue was washed with H_2O, dried, and crystallized. (See Table II.)

***N*-(4-Acetylphenyl)-3-[4-(5-bromo-2-pyridinyl)-1-piperazinyl]propanamide (18) (Method E).** A solution of bromine (3.2 g, 20 mmol) in AcOH (30 mL) was added dropwise (20 min at 18–23 °C) to a well-stirred solution of *N*-(4-acetylphenyl)-3-[4-(2-pyridinyl)-1-piperazinyl]propanamide (**17**; 7.04 g, 20 mmol) in AcOH (150 mL) and Ac_2O (1 mL). After stirring

Table II. *N*-(Substituted phenyl)-ω-[4-(2-pyridinyl)-1-piperazinyl]alkanamides



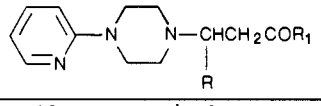
compd	*n*	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	method[a]	yield, %	recryst[b] solvent	mp, °C	formula	anal.
5	2	H	CH_3	H	H	H	CH_3	H	H	C[c]	68	Et	121–122	$C_{20}H_{26}N_4O$	C, H, N
												E95 + A	134	$C_{20}H_{26}N_4O\cdot 2HCl\cdot H_2O$	C, H, N, Cl, H_2O
8	1	H	CH_3	H	H	H	CH_3	H	H	D	54	Et	144–145	$C_{19}H_{24}N_4O$	C, H, N
												E95	189–191	$C_{19}H_{24}N_4O\cdot 2HCl\cdot H_2O$	C, H, N, Cl, H_2O
9	2	H	H	H	H	H	H	H	H	C[c]	64	Et + H	79–81	$C_{18}H_{22}N_4O$	C, H, N
10	2	H	CH_3	H	H	H	H	H	H	C[c]	59	E	99–102	$C_{19}H_{24}N_4O$	C, H, N
												E95	201–202	$C_{19}H_{24}N_4O\cdot 2HCl\cdot H_2O$	C, H, N, Cl, H_2O
11	2	H	CH_3	CH_3	H	CH_3	CH_3	H	H	C[d]	75	Et	176–178	$C_{22}H_{30}N_4O$	C, H, N
												E95	176–181	$C_{22}H_{30}N_4O\cdot 2HCl\cdot 2H_2O$	C, H, N, Cl, H_2O
12	1	H	CH_3	CH_3	H	CH_3	CH_3	H	H	D[e]	51	Et	151–152	$C_{21}H_{28}N_4O$	C, H, N
13	2	H	Cl	H	H	H	H	H	H	C[c]	63	E	95–96	$C_{18}H_{21}ClN_4O$	C, H, N, Cl
												E95	181–185	$C_{18}H_{21}ClN_4O\cdot 2HCl\cdot H_2O$	C, H, N, Cl, H_2O
14	2	H	Cl	H	H	H	Cl	H	H	C	76	Et	155–157	$C_{18}H_{20}Cl_2N_4O$	C, H, N, Cl
												E	270–272	$C_{18}H_{20}Cl_2N_4O\cdot 2HCl$	C, H, N, Cl
15	2	H	$COCH_3$	H	H	H	H	H	H	C[f]	77	B + H	90–91	$C_{20}H_{24}N_4O_2$	C, H, N
												E95	230–232	$C_{20}H_{24}N_4O_2\cdot 2HCl\cdot {}^1/_2H_2O$	C, H, N, Cl, H_2O
16	2	H	H	$COCH_3$	H	H	H	H	H	C[f]	73	E	109–111	$C_{20}H_{24}N_4O_2$	C, H, N
												E80	223–225	$C_{20}H_{24}N_4O_2\cdot 2HCl\cdot H_2O$	C, H, N, Cl, H_2O
17	2	H	H	H	$COCH_3$	H	H	H	H	C[g]	55	E40	134–136	$C_{20}H_{24}N_4O_2\cdot {}^1/_2H_2O$	C, H, N, Cl, H_2O
												M + W	235–240	$C_{20}H_{24}N_4O_2\cdot 2HCl\cdot {}^1/_2H_2O$	C, H, N, Cl, H_2O
18	2	H	H	H	$COCH_3$	H	H	Br	H	E	52	Et	190–191	$C_{20}H_{23}BrN_4O_2$	C, H, N, Br
												W	231–234	$C_{20}H_{23}BrN_4O_2\cdot HBr\cdot H_2O$	C, H, N, Br, H_2O
19	2	H	NO_2	H	H	H	H	H	H	C[j]	72	T + H	90–92	$C_{18}H_{21}N_5O_3$	C, H, N
												E90	220–222	$C_{18}H_{21}N_5O_3\cdot 2HCl$	C, H, N, Cl
20	2	H	H	NO_2	H	H	H	H	H	C	89	T	133–134	$C_{18}H_{21}N_5O_3$	C, H, N
												E90	228–230	$C_{18}H_{21}N_5O_3\cdot 2HCl$	C, H, N, Cl
21	2	H	H	H	NO_2	H	H	H	H	C[c]	69	Dx	157–158	$C_{18}H_{21}N_5O_3$	C, H, N
												E90	242–244	$C_{18}H_{21}N_5O_3\cdot 2HCl\cdot H_2O$	C, H, N, Cl, H_2O
22	2	H	NO_2	H	H	H	H	H	OCH_3	C[j]	56	E	103–104	$C_{19}H_{23}N_5O_4$	C, H, N
												M	212–213	$C_{19}H_{23}N_5O_4\cdot HCl$	C, H, N, Cl
23	2	CH_3	H	H	NO_2	H	H	H	H	C	66	E	129–130	$C_{19}H_{23}N_5O_3\cdot {}^1/_2H_2O$	C, H, N, Cl, H_2O
												E90	210–212	$C_{19}H_{23}N_5O_3\cdot 2HCl\cdot 2H_2O$	C, H, N, Cl, H_2O
24	2	H	H	H	NO_2	H	H	H	OCH_3	C	71	E	126–128	$C_{19}H_{23}N_5O_4$	C, H, N
												E90	207–211	$C_{19}H_{23}N_5O_4\cdot HCl$	C, H, N, Cl
25	2	H	NH_2	H	H	H	H	H	H	B[h]	68	T	149–150	$C_{18}H_{23}N_5O$	C, H, N
26	2	H	H	NH_2	H	H	H	H	H	B[h]	71	E	148–150	$C_{18}H_{23}N_5O$	C, H, N
												E90	230–231	$C_{18}H_{23}N_5O\cdot 3HCl\cdot {}^1/_2H_2O$	C, H, N, Cl, H_2O
27	2	H	H	H	NH_2	H	H	H	H	B[f]	73	Et	103–104	$C_{18}H_{23}N_5O$	C, H, N
28	2	CH_3	H	H	NH_2	H	H	H	H	B[i]	56	E90	268–270	$C_{19}H_{25}N_5O\cdot 3HCl$	C, H, N, Cl
29	2	H	NH_2	H	H	H	H	H	OCH_3	B	82	Et	148–150	$C_{19}H_{25}N_5O_2$	C, H, N
												E95	179 dec.	$C_{19}H_{25}N_5O_2\cdot 2HCl$	C, H, N, Cl
30	2	H	H	H	NH_2	H	H	H	OCH_3	B[h]	74	E	96–98	$C_{19}H_{25}N_5O_2\cdot {}^1/_2H_2O$	C, H, N, Cl, H_2O
												E90	207	$C_{19}H_{25}N_5O_2\cdot 2HCl\cdot {}^3/_2H_2O$	C, H, N, Cl, H_2O
31	2	H	H	CF_3	H	H	H	H	H	C	60	E	197–200	$C_{19}H_{21}F_3N_4O\cdot 2HCl$	C, H, N, Cl, F
32	2	H	H	OCH_3	H	H	H	H	H	C	73	Et	102–103	$C_{19}H_{24}N_4O_2$	C, H, N
												E90	224–225	$C_{19}H_{24}N_4O_2\cdot 2HCl\cdot {}^1/_2H_2O$	C, H, N, Cl, H_2O
33	2	H	H	H	OCH_3	H	H	H	H	C[c]	74	E	127–128	$C_{19}H_{24}N_4O_2$	C, H, N
												E95	207–211	$C_{19}H_{24}N_4O_2\cdot 2HCl\cdot {}^1/_2H_2O$	C, H, N, Cl, H_2O
34	2	H	H	H	OC_2H_5	H	H	H	H	C[c]	65	E	129–130	$C_{20}H_{26}N_4O_2$	C, H, N
												E95	228–229	$C_{20}H_{26}N_4O_2\cdot HCl$	C, H, N, Cl
35	2	H	H	H	SCH_3	H	H	H	H	C	66	E	128–129	$C_{19}H_{24}N_4OS$	C, H, N

Table II (Continued)

compd	n	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	method[a]	yield, %	recryst[b] solvent	mp, °C	formula	anal.
36	2	H	H	H	$SCH(CH_3)_2$	H	H	H	H	C[j]	76	Et	99–103	$C_{21}H_{28}N_4OS$	C, H, N
37	2	H	H	H	CN	H	H	H	H	C[k]	78	E	112–114	$C_{19}H_{21}N_5O$	C, H, N
												E90	247–248	$C_{19}H_{21}N_5O{\cdot}2HCl$	C, H, N, Cl
38	2	H	H	H	$CONH_2$	H	H	H	H	C[k]	72	E	227–228	$C_{19}H_{23}N_5O_2$	C, H, N
												E90	252–254	$C_{19}H_{23}N_5O_2{\cdot}2HCl{\cdot}{}^5/_2H_2O$	C, H, N, Cl, H_2O
39	2	H	H	H	$CH(OH)CH_3$	H	H	H	H	F	49	E	157–161	$C_{20}H_{26}N_4O_2$	C, H, N
40	2	H	H	H	$COOC_2H_5$	H	H	H	H	C[c,h]	37	Et	92–95	$C_{21}H_{26}N_4O_3$	C, H, N
												M	227–229	$C_{21}H_{26}N_4O_3{\cdot}2HCl$	C, H, N, Cl
41	2	H	H	H	Cl	H	H	H	H	C[c]	67	E	118–119	$C_{18}H_{21}ClN_4O$	C, H, N, Cl
												E95	202–203	$C_{18}H_{21}ClN_4O{\cdot}2HCl{\cdot}H_2O$	C, H, N, Cl, H_2O
42	2	H	H	H	OH	H	H	H	H	C	76	E80	189–190	$C_{18}H_{22}N_4O_2$	C, H, N
												E90	228–230	$C_{18}H_{22}N_4O_2{\cdot}2HCl$	C, H, N, Cl
43	2	H	H	H	$NHCOCH_3$	H	H	H	H	G	75	E	187–188	$C_{20}H_{25}N_5O_2$	C, H, N
												E90	190–210	$C_{20}H_{25}N_5O_2{\cdot}2HCl$	C, H, N, Cl
44	2	H	H	H	$NHCOC_2H_5$	H	H	H	H	G	76	E	195–197	$C_{21}H_{27}N_5O_2$	C, H, N
												E90	190–192	$C_{21}H_{27}N_5O_2{\cdot}2HCl{\cdot}H_2O$	C, H, N, Cl, H_2O
45	2	H	H	H	$NHCOCOOC_2H_5$	H	H	H	H	H	61	E	157–158	$C_{22}H_{27}N_5O_4$	C, H, N
46	2	H	H	H	$NHCONH_2$	H	H	H	H	I	16	M	207–208	$C_{19}H_{24}N_6O_2$	C, H, N
47	2	H	H	H	$NHCONHCH_3$	H	H	H	H	L	69	M	213–214	$C_{20}H_{26}N_6O_2$	C, H, N
												E80	209–212	$C_{20}H_{26}N_6O_2{\cdot}2HCl{\cdot}{}^1/_2H_2O$	C, H, N, Cl, H_2O
48	2	H	H	H	$NHCONHC_6H_5$	H	H	H	H	L	73	Dx + W	>260	$C_{25}H_{28}N_6O_2$	C, H, N
49	2	H	H	H	SO_2NH_2	H	H	H	H	C[k]	77	M	207–211	$C_{18}H_{23}N_5O_3S$	C, H, N, S

[a] See the Experimental Section. [b] A = Me_2CO, B = C_6H_6, Dx = 1,4-dioxane, E = EtOH, E## = ##% EtOH, Et = EtOAc, H = hexane, M = MeOH, T = toluene, W = H_2O. [c] The reaction was carried out in refluxing C_6H_6. [d] The reaction was carried out in xylenes at 120 °C for 9 h. [e] The reaction was carried out in refluxing *i*-PrOH. [f] Purified by column chromatography, $CHCl_3$/MeOH (49:1). [g] Purified by column chromatography, EtOAc/MeOH (7:3). [h] Purified by column chromatography, $CHCl_3$. [i] Purified by column chromatography, $CHCl_3$/MeOH (from 99:1 to 95:5). [j] The corresponding *N*-phenylprop-2-enamide intermediate, previously unknown, was used as crude, characterized by NMR only. [k] The reaction was carried out in Me_2SO at 50 °C for 16 h, the mixture was pured in cold H_2O, and the crude was collected by suction.

Table III. 3-[4-(2-Pyridinyl)-1-piperazinyl]alkanoyl Derivatives



compd	R	R_1	method[a]	yield, %	recryst[b] solvent	mp, °C	formula	anal.
50	H	OH	C[c]	66	E	182–184	$C_{12}H_{17}N_3O_2$	C, H, N
51	H	OCH_3	C[d]	68	H	56–58	$C_{13}H_{19}N_3O_2$	C, H, N
					I	191	$C_{13}H_{19}N_3O_2{\cdot}HCl$	C, H, N, Cl
52	H	OCH_2CH_3	C[e,f]	54	E	147–149[g]	$C_{14}H_{21}N_3O_2{\cdot}2HCl{\cdot}H_2O$	C, H, N, Cl, H_2O
53	H	$OCH_2CH{=}CH_2$	C[d,h]	40	E	169–173	$C_{15}H_{21}N_3O_2{\cdot}2HCl$	C, H, N, Cl
54	H	NH_2	C[d]	70	E95	215–216	$C_{12}H_{18}N_4O{\cdot}2HCl$	C, H, N, Cl
55	CH_3	OCH_3	C[e,f]	44	E	115–118	$C_{14}H_{21}N_3O_2{\cdot}2C_4H_4O_4$	C, H, N
56	CH_3	OCH_2CH_3	C[e,f]	38	E + D	181–182	$C_{15}H_{23}N_3O_2{\cdot}2HCl$	C, H, N, Cl

[a] See the Experimental Section. [b] D = Et_2O, E = EtOH, E95 = 95% EtOH, H = hexane, I = *i*-PrOH. [c] The reaction was carried out in refluxing C_6H_6. [d] The reaction was carried out without solvent at 20–25 °C. [e] The reaction was carried out without solvent at 40 °C. [f] Purified by column chromatography, EtOAc. [g] The anhydrous dihydrochloride melts at 181–183 °C. [h] The compound, as dihydrochloride, was purified by column chromatography, eluting with the upper phase of the mixture *n*-BuOH/H_2O/AcOH, 4:5:1.

for 1 h, the solution was poured into H_2O (400 mL) and the precipitate was collected by suction. The crude monohydrobromide (8.2 g) was dissolved in warm MeOH (500 mL), and dilute NaOH was added until the solution was alkaline. After cooling and dilution with H_2O (500 mL), the resulting solid base was collected and crystallized. (See Table II.)

***N*-[4-(1-Hydroxyethyl)phenyl]-3-[4-(2-pyridinyl)-1-piperazinyl]propanamide (39) (Method F).** $NaBH_4$ (1.52 g, 40 mmol) was added portionwise to a stirred solution of *N*-(4-acetylphenyl)-3-[4-(2-pyridinyl)-1-piperazinyl]propanamide (**17**; 14.8 g, 40 mmol) in EtOH (280 mL) at 20–25 °C, and stirring was continued for 8 h. After standing overnight, the crude precipitate was collected and suspended in H_2O. The suspension was slightly acidified with dilute HCl and stirred for 1 h at 20–25 °C. The mixture was alkalinized with 5% aqueous $NaHCO_3$ and extracted with $CHCl_3$ (500 mL). The organic phase was separated and dried, the solvent evaporated, and the residue crystallized. (See Table II.)

***N*-[4-(Acetylamino)phenyl]-3-[4-(2-pyridinyl)-1-piperazinyl]propanamide (43) (Method G).** Ac_2O (2.04 g, 20 mmol) was added to a solution of *N*-(4-aminophenyl)-3-[4-(2-pyridinyl)-1-piperazinyl]propanamide (**27**; 6.5 g, 20 mmol) in $CHCl_3$ (20 mL), and the solution was stirred under reflux for 6 h. After cooling, the crude precipitate was collected, dried, and dissolved in EtOH, and HCl in EtOH was added until acidic pH was reached. The crude hydrochloride precipitate was collected and crystallized. The corresponding base was obtained by adding aqueous Na_2CO_3 to an aqueous solution of the hydrochloride: the resulting precipitate was collected, dried, and crystallized. (See Table II.)

***N*-[4-(Ethoxalylamino)phenyl]-3-[4-(2-pyridinyl)-1-piperazinyl]propanamide (45) (Method H).** Ethoxalyl chloride (4.1 g, 30 mmol) was added dropwise under cooling (0–7 °C) to a stirred solution of *N*-(4-aminophenyl)-3-[4-(2-pyridinyl)-1-piperazinyl]propanamide (**27**; 8.13 g, 25 mmol) in $CHCl_3$ (50 mL) containing Et_3N (4.2 mL, 30 mmol). After the mixture was allowed to stand overnight at 20–25 °C, $Et_3N{\cdot}HCl$ was separated by filtration, the solvent was evaporated in vacuo, and the residue was suspended in H_2O, collected by suction, dried, and crystallized. (See Table II.)

***N*-[4-[(Aminocarbonyl)amino]phenyl]-3-[4-(2-pyridinyl)-1-piperazinyl]propanamide (46) (Method I).** KCNO (1.64 g, 20 mmol) was added at 20–25 °C to a stirred solution of *N*-(4-aminophenyl)-3-[4-(2-pyridinyl)-1-piperazinyl]propanamide (**27**; 3.25 g, 10 mmol) in 1 N HCl (50 mL), and stirring was continued for 8 h. After the mixture was

Table IV. Pharmacological Activity of 1-(2-Pyridinyl)piperazine Derivatives[a]

compd	mouse LD_{50},[b] mmol/kg		rat PCA test, ID_{50},[b] μmol/kg		antibroncho-spastic act. ID_{75}, μmol/kg	mast cell degradn	
	ip	po	ip	po	iv	inhibn, %	dose, μmol/kg iv
2	0.54 (0.47–0.85)		>175		8.15		
3	0.55 (0.39–0.76)		>167		5.27		
4[c]	0.71 (0.63–1.05)		>236		8.39		
5	0.81 (0.67–1.21)		8 (2–34)	86 (60–123)	1.57	27	45
6	0.53 (0.39–0.70)		78 (26–134)		4.60		
7	0.32 (0.27–0.43)		30 (6–147)				
8	0.90 (0.72–1.13)		123 (81–186)		>24.00		
9[c]	1.16 (0.97–1.74)	1.35 (0.97–1.87)	53 (35–79)	72 (26–199)	1.93	12	32
10	1.01 (0.72–1.40)	1.58 (1.35–1.88)	65 (22–195)	>96	0.47		
11	0.57 (0.50–0.84)		18 (14–22)	26 (9–81)	1.56	2	42
12	0.65 (0.56–0.94)		>212		>23.50		
13	1.29 (0.96–1.77)	2.64 (1.72–3.90)	70 (40–122)	199 (119–331)	1.12	0	32
14	0.80 (0.66–1.19)	1.24 (0.93–1.70)	85 (78–93)		0.40		
15	2.30 (1.73–3.04)	>6.91	77 (57–105)	>230	0.89	0	29
16	0.68 (0.54–0.99)	1.11 (0.94–1.65)	73 (65–82)		0.20		
17	0.48 (0.41–0.93)	1.50 (1.30–1.80)	49 (42–57)		0.02		
18[c]	NA[d]	>7.00	43 (20–94)	>230	NT[e]		
19	2.08 (1.41–3.07)	3.70 (3.02–4.51)	>230		0.58		
20	0.42 (0.30–0.61)	2.07 (1.75–2.99)	58 (42–79)	137 (99–191)	0.37	87	23
21	0.47 (0.40–0.72)	0.81 (0.67–1.21)	27 (21–35)		0.94		
22	NA[d]	>7.10	>237		0.52		
23	0.42 (0.29–0.60)	1.20 (0.86–1.66)	61 (25–150)		1.75		
24	NA[d]	4.39 (3.08–6.27)	130 (59–287)	204 (145–288)	0.16		
25[c]	3.20 (0.96–10.62)	2.08 (1.79–2.41)	100 (78–129)		1.63	26	61
26	0.90 (0.85–1.18)	0.85 (0.68–1.24)	148 (114–193)		0.61		
27[c]	1.11 (0.92–1.65)	1.29 (0.92–1.78)	23 (11–48)	91 (72–115)	0.02	84	31
28	1.19 (1.00–1.40)	2.97 (2.50–3.50)	35 (24–51)	92 (13–117)	0.59	14	45
29	0.37 (0.27–0.50)	0.67 (0.53–0.84)	44 (28–69)		1.08		
30	0.53 (0.48–0.77)	1.60 (1.23–1.71)	56 (45–69)	106 (80–141)	0.40		
31	0.56 (0.43–0.73)	1.17 (0.84–1.62)	>55		0.65		
32	1.18 (1.02–1.35)	7.10 (5.68–7.37)	>118		0.56		
33	0.71 (0.57–1.04)	1.16 (0.99–1.61)	48 (43–53)	>95	0.24	19	47
34	0.69 (0.61–0.99)	0.92 (0.77–1.28)	37 (34–42)		0.14	0	26
35[c]	NA[d]	>8.40	57 (30–108)	171 (141–206)	0.17	50	28
36[c]	1.14 (0.94–1.40)	2.18 (1.63–2.93)	>120	>221	0.80		
37	0.39 (0.28–0.52)	0.62 (0.41–0.93)	>39		0.64		
38	NA[d]	>6.40	124 (44–250)	>212	0.30		
39[c]	3.25 (2.17–4.89)	5.97 (5.08–7.62)	32 (23–45)	103 (80–130)	0.48	22	28
40	0.66 (0.53–0.97)	0.92 (0.66–1.27)	30 (23–40)	107 (88–129)	0.17	83	22
41	0.62 (0.55–1.17)	0.96 (0.69–1.33)	43 (35–51)	>96	2.27	0	48
42	NA[d]	5.20 (4.50–5.90)	161 (128–203)	189 (161–222)	0.49	64	50
43	NA[d]	>6.81	90 (57–142)	153 (110–212)	0.97	29	45
44	1.05 (0.89–1.65)	1.53 (1.19–2.07)	147 (66–231)		0.23		
45[c]	NA[d]	>7.05	127 (115–142)		0.23	7	35
46[c]	NA[d]	>8.10	194 (154–246)	>271	0.25		
47	NA[d]	>6.50	109 (95–124)	>220	0.29	0	43
48[c]	NA[d]	>6.70	>225		0.31		
49[c]	NA[d]	>7.70	>257		0.19		
50[c]	5.53 (4.25–7.74)		>1277		5.23		
51	4.02 (3.43–5.07)		252 (206–307)		3.50		
52	5.08 (3.67–6.20)		665 (328–1350)		7.03		
53	1.03 (0.86–1.55)	>8.61	330 (213–512)		11.49		
54	2.44 (1.82–3.42)		203 (99–415)	260 (184–369)	2.47	23	65
55	1.35 (1.13–1.82)		>404		2.37		
56	6.85 (5.14–9.14)		>857		4.14		
DSCG	NA[d]	>6.41	60 (41.2–87.3)	>640	>21.00	83	43
oxatomide	NA[d]	>7.30		9 (8–11)	0.08	40	23
ketotifen	0.35 (0.29–0.42)	0.58 (0.50–0.68)		2 (1.7–2.4)	0.0015	22	2[f]

[a] For iv administration, the compounds were dissolved in saline or HCl-added saline (pH 3.5–4). For ip and po administration the compounds were dissolved or suspended in 10% aqueous acacia gum. The compounds were tested as salts; see Tables I–III, unless otherwise noted. [b] 95% confidence limits are given in parentheses. [c] Tested as base. [d] Poorly adsorbed at the dose of 1000 mg/kg. [e] Not tested because of poor solubility. [f] Higher doses induced degranulation.

allowed to stand overnight, aqueous Na_2CO_3 was added to the ice-cooled solution and the precipitate was collected by suction and dried. The solid was purified by repeated column chromatography on silica gel, eluting with $CHCl_3$/MeOH (from 98:2 to 1:1). The fractions containing the pure product were combined, the solvents were evaporated, and the residue was crystallized. (See Table II.)

***N*-[4-[[[(Aminocarbonyl)amino]carbonyl]amino]-phenyl]-3-[4-(2-pyridinyl)-1-piperazinyl]propanamide** was isolated, as the less retained main byproduct, in the course of the chromatographic purification of **46** and crystallized from MeOH: yield 3%; mp 198–199 °C. Anal. ($C_{20}H_{25}N_7O_3$) C, H, N.

***N*-[4-[[(Methylamino)carbonyl]amino]phenyl]-3-[4-(2-pyridinyl)-1-piperazinyl]propanamide (47) (Method L).** A mixture of *N*-(4-aminophenyl)-3-[4-(2-pyridinyl)-1-piperazinyl]-propanamide (**27**; 6.5 g, 20 mmol) and methyl isocyanate (2.24 g, 40 mmol) in toluene (60 mL) at 20–25 °C was stirred for 8 h. The solvent was evaporated in vacuo from the jelly-like mass and the residue was crystallized. (See Table II.)

***N*-(2,6-Dimethylphenyl)-2-propenamide.** 2-Propenoyl

chloride (8.8 mL, 100 mmol) was added dropwise under stirring to a solution of 2,6-dimethylbenzenamine (12.32 mL, 100 mmol) in AcOH (80 mL), maintaining the temperature near 10 °C. At the end of the addition, $NaOAc \cdot 3H_2O$ (33 g, 240 mmol) in H_2O (150 mL) was added and the mixture was stirred 1 h at room temperature and then poured in H_2O (250 mL). After standing overnight, the precipitate was collected by suction, dried, and crystallized from EtOAc to afford 9 g (51%) of the title product: mp 143–144 °C. Anal. ($C_{11}H_{13}NO$) C, H, N.

In the same manner, the following new intermediates were prepared (yield percent, melting point, crystallization solvent, formula, elemental analysis): ***N*-(2,3,5,6-tetramethylphenyl)-2-propenamide** (**55**, 181–182 °C, C_6H_6, $C_{13}H_{17}NO$, C, H, N); ***N*-(2-acetylphenyl)-2-propenamide** (**51**, 65–66 °C, hexane, $C_{11}H_{11}NO_2$, C, H, N); ***N*-(3-acetylphenyl)-2-propenamide** (**61**, 115–116 °C, toluene, $C_{11}H_{11}NO_2$, C, H, N); ***N*-(4-acetylphenyl)-2-propenamide** (**61**, 147–148 °C, C_6H_6, $C_{11}H_{11}NO_2$, C, H, N.

Acute Toxicity. Female albino mice weighing 20–30 g were employed. Test compounds were administered as solutions or suspensions in 10% aqueous acacia gum. LD_{50} values were determined both intraperitoneally and orally (10 animals/dose). The mortality rate was recorded over a 7-day period. LD_{50} values and 95% confidence limits were calculated by the method of Bliss, computerized according to the indication reported by Rosiello et al.[12]

Rat PCA Test. The method used was similar to that described by Goose and Blair.[9] Female albino rats weighing 200–250 g were treated intramuscularly with 1% egg albumin in 0.9% NaCl (1 mL) and intraperitoneally with Haemophilus pertussis vaccine (2×10^{10} organisms). Twelve days after the treatment the animals were bled, and serum was collected. Another group of rats was sensitized at ventral site by intradermal injection of the antialbumin antiserum. Twenty-four hours later, groups of 10 rats were given either vehicle (10% acacia gum, 10 mL/kg) or test compounds dissolved or suspended in the vehicle. Thirty minutes after intraperitoneal or 60 min after oral administration of the test compound, rats were challenged intravenously with 0.3% egg albumin in 0.9% NaCl (0.2 mL) and 1% Evans blue dye (0.5 mL). Thirty minutes after antigen challenge the animals were sacrificed, ventral skins were reflected, and blued areas were measured. Mean values for areas in control and drug-treated groups were determined. The 50% inhibition of spot areas (ID_{50}) and 95% confidence limits were calculated by regression analysis.

Histamine-Induced Bronchospasm in Guinea Pigs. The antibronchospastic activity was investigated according to the Konzett and Rössler method.[10] Guinea pigs of either sex weighing 300–350 g were anaesthesized with ethylurethane (1.5 g/kg) intraperitoneally. Bronchospasm was induced by intravenous administration of histamine dihydrochloride (0.5–2.5 μg/kg) in 0.9% NaCl (1 mL/kg). Test compounds were dissolved in saline alone or by addition of a slight excess of HCl or CH_3SO_3H (pH of the solution 3.5–4) and administered intravenously (1 mL/kg) 1 min before the agonist administration. The compounds were tested in duplicate at three concentrations that caused inhibitory effects between 20 and 90%. The ID_{75} values were graphically calculated from the log dose–response curves.

Compound 48/80 Induced Degranulation of Rat Mesenteric Mast Cells. Inhibition of compound 48/80 induced degranulation was assessed by the method of Fawcett.[11] Female albino rats weighing 180–200 g were employed. Tyrode solution, or Tyrode solution containing varying concentrations of compound 48/80 (from 0.1 to 1 μg/mL), were injected into the peritoneal cavity in 10-mL amounts. The compounds were dissolved in the same manner as reported for the guinea pig bronchospasm test and administered intravenously (1 mL/kg) 1 min before compound 48/80. Fifteen minutes later, the animals were sacrificed and a small segment of mesentery was withdrawn. The mesenteries were placed on glass slides and were fixed and stained.

Microscopic examination of the mesenteries was made, and mast cell degranulation was measured by counting the percentage of 200 cells that showed disruption and loss of granules.[9] The mean percentage of degranulation from five replicate animals in control and drug-treated groups was evaluated, and the percent inhibition of mast cells disruption for given doses was calculated.

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Registry No. **2**, 104374-01-8; **2**·2HCl, 104373-48-0; **3**, 104374-02-9; **3**·3HCl, 104373-49-1; **4**, 104373-50-4; **5**, 86523-87-7; **5**·2HCl, 104373-51-5; **6**, 104374-03-0; **6**·2HCl, 104373-52-6; **6** (acid chloride), 39728-43-3; **7**, 104374-04-1; **7**·2HCl, 104373-53-7; **7** (acid chloride), 99859-96-8; **8**, 86523-70-8; **8**·2HCl, 104373-54-8; **9**, 86523-85-5; **10**, 86523-86-6; **10**·2HCl, 104373-55-9; **11**, 86523-84-4; **11**·2HCl, 104373-56-0; **12**, 86523-71-9; **13**, 86524-01-8; **13**·2HCl, 104373-57-1; **14**, 86524-04-1; **14**·2HCl, 104373-58-2; **15**, 86524-06-3; **15**·2HCl, 104373-59-3; **16**, 86524-07-4; **16**·2HCl, 104373-60-6; **17**, 86523-82-2; **17**·2HCl, 104373-61-7; **18**, 104374-05-2; **18**·HBr, 104373-62-8; **19**, 86523-97-9; **19**·2HCl, 104373-63-9; **20**, 86523-73-1; **20**·2HCl, 104373-64-0; **21**, 86523-75-3; **21**·2HCl, 104373-65-1; **22**, 86524-02-9; **22**·HCl, 104373-66-2; **23**, 86523-98-0; **23**·2HCl, 104373-67-3; **24**, 86523-99-1; **24**·HCl, 104373-68-4; **25**, 86523-91-3; **26**, 86523-92-4; **26**·3HCl, 104373-69-5; **27**, 86523-76-4; **28**, 104373-70-8; **28**·3HCl, 104374-06-3; **29**, 86546-13-6; **29**·2HCl, 104373-71-9; **30**, 86523-93-5; **30**·2HCl, 104373-72-0; **31**, 86524-05-2; **31**·2HCl, 104373-73-1; **32**, 86524-12-1; **32**·2HCl, 104373-74-2; **33**, 86523-72-0; **33**·2HCl, 104373-75-3; **34**, 86523-88-8; **34**·HCl, 104373-76-4; **35**, 86524-09-6; **36**, 104373-77-5; **37**, 86524-10-9; **37**·2HCl, 104373-78-6; **38**, 86524-11-0; **38**·2HCl, 104373-79-7; **39**, 86523-83-3; **40**, 86524-08-5; **40**·2HCl, 104393-11-5; **41**, 86524-03-0; **41**·2HCl, 104373-80-0; **42**; **42**·2HCl, 104373-81-1; **43**, 86523-95-7; **43**·2HCl, 104373-82-2; **44**, 86523-80-0; **44**·2HCl, 104373-83-3; **45**, 86523-81-1; **46**, 86523-79-7; **47**, 86523-96-8; **47**·2HCl, 104373-84-4; **48**, 86523-77-5; **49**, 86523-78-6; **50**, 104373-85-5; **51**, 104374-08-5; **51**·HCl, 104373-86-6; **52**, 104374-09-6; **52**·2HCl, 104373-87-7; **53**, 104374-10-9; **53**·2HCl, 104373-88-8; **54**, 104374-11-0; **54**·2HCl, 104373-89-9; **55**, 104373-90-2; **55**·$2C_4H_4O_4$, 104373-91-3; **56**, 104374-12-1; **56**·2HCl, 104373-92-4; 2,6-$(CH_3)_2C_6H_3NHCOCH{=}CH_2$, 104373-94-6; $C_6H_5NHCOCH{=}CH_2$, 2210-24-4; 2-$CH_3C_6H_4NHCOCH{=}CH_2$, 17090-19-6; 2,3,5,6-$(CH_3)_4NHCOCH{=}CH_2$, 104373-95-7; 2-$ClC_6H_4NHCOCH{=}CH_2$, 17090-09-4; 2,6-$Cl_2C_6H_3NHCOCH{=}CH_2$, 37511-45-8; 2-$CH_3COC_6H_4NHCOCH{=}CH_2$, 104373-96-8; 3-$CH_3COC_6H_4NHCOCH{=}CH_2$, 104373-97-9; 4-$CH_3COC_6H_4NHCOCH{=}CH_2$, 22535-53-1; 2-$O_2NC_6H_4NHCOCH{=}CH_2$, 104373-98-0; 3-$O_2NC_6H_4NHCOCH{=}CH_2$, 17090-15-2; 4-$O_2NC_6H_4NHCOCH{=}CH_2$, 7766-38-3; 3-$F_3CC_6H_4NHCOCH{=}CH_2$, 1794-20-3; 3-$CH_3OC_6H_4NHCOCH{=}CH_2$, 17208-99-0; 4-$CH_3OC_6H_4NHCOCH{=}CH_2$, 7766-37-2; 4-$CH_3CH_2OC_6H_4NHCOCH{=}CH_2$, 2918-94-7; 4-$CH_3SC_6H_4NHCOCH{=}CH_2$, 27817-73-8; 4-$(CH_3)_2CHSC_6H_4$-$NHCOCH{=}CH_2$, 104373-99-1; 4-$NCC_6H_4NHCOCH{=}CH_2$, 90842-07-2; 4-$H_2NCOC_6H_4NHCOCH{=}CH_2$, 17090-31-2; 4-$CH_3CH_2OCOC_6H_4NHCOCH{=}CH_2$, 14745-58-5; 4-$ClC_6H_4NHCOCH{=}CH_2$, 5453-48-5; 4-$HOC_6H_4NHCOCH{=}CH_2$, 34443-04-4; 4-$H_2NSO_2C_6H_4NHCOCH{=}CH_2$, 2621-99-0; $H_2C{=}CHCO_2H$, 79-10-7; $H_2C{=}CHCO_2CH_3$, 96-33-3; $H_2C{=}CHCO_2C$-H_2CH_3, 140-88-5; $H_2C{=}CHCO_2CH_2CH{=}CH_2$, 999-55-3; $H_2C{=}$$CHCONH_2$, 79-06-1; $H_3CCH{=}CHCO_2CH_3$, 18707-60-3; H_3CC-$H{=}CHCO_2CH_2CH_3$, 10544-63-5; aziridine, 151-56-4; 2-butoxy-4-quinolinecarbonyl chloride, 10249-04-4; *N*-(2-butoxy-4-quinolinecarbonyl)aziridine, 104373-93-5; 1-(2-pyridinyl)piperazine, 34803-66-2; 3-methyl-1-(2-pyridinyl)piperazine, 63286-11-3; 1-(6-methoxy-2-pyridinyl)piperazine, 51047-54-2; 2,6-$(CH_3)_2C_6H_3NHCOCH_2Cl$, 1131-01-7; ethoxalyl chloride, 4755-77-5; *N*-[4-[[[(aminocarbonyl)amino]carbonyl]amino]phenyl]-3-[4-(2-pyridinyl)-1-piperazinyl]propanamide, 104374-00-7; 2-propenoyl chloride, 814-68-6; 2,6-dimethylbenzenamine, 87-62-7; 2,3,5,6-tetramethylbenzenamine, 2217-46-1; 2-acetylbenzenamine, 551-93-9; 3-acetylbenzenamine, 99-03-6; 4-acetylbenzenamine, 99-92-3.

Supplementary Material Available: QSAR calculations and tables containing the values of the independent variables used for QSAR study and the correlation coefficients between parameters (5 pages). Ordering information is given on any current masthead page.

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