Acrylamide Derivatives as Antiallergic Agents. I. Synthesis and Structure–Activity Relationships of *N*-[(4-Substituted 1-piperazinyl)alkyl]-3-(aryl and heteroaryl)acrylamides

Yoshinori NISHIKAWA,* Tokuhiko SHINDO, Katsumi ISHII, Hideo NAKAMURA, Tatsuya KON and Hitoshi UNO

Research Laboratories, Dainippon Pharmaceutical Co., Ltd., Enoki 33–94, Suita, Osaka 564, Japan. *Received June 20, 1988*

A new series of acrylamide derivatives (7—10) were synthesized. Antiallergic activity of these compounds was evaluated and their structure–activity relationships were examined. Compound 10d, *N*-[4-(4-diphenylmethyl-1-piperazinyl)butyl]-3-(3-pyridyl)acrylamide, showed antiallergic activity equivalent or superior to that of ketotifen in the rat passive cutaneous anaphylaxis (PCA) test by oral administration. Compound 10d, unlike ketotifen, had more potent *in vitro* 5-lipoxygenase inhibitory activity than caffeic acid, whereas its *in vitro* antihistamine activity was weaker than that of ketotifen. In addition, its inhibitory activity against histamine release from rat mast cells was approximately two-thirds as potent as that of disodium cromoglycate (DSCG). Compound 10d is a promising agent for treating a variety of allergic diseases.

Keywords *N*-[(4-substituted 1-piperazinyl)alkyl]cinnamamide; *N*-[4-(4-diphenylmethyl-1-piperazinyl)butyl]-3-heteroarylacrylamide; antiallergic agent; anti-PCA activity; 5-lipoxygenase inhibitory activity; histamine-release inhibitory activity; antihistamine activity

Disodium cromoglycate (DSCG)[1] shows inhibitory activity against chemical mediator release from sensitized mast cells, and has been clinically successful for the prophylactic treatment of bronchial asthma. Subsequently, many drugs with antiallergic activity have been developed. Although the action mechanisms of these drugs have not yet been elucidated thoroughly, the antiallergic activity of some drugs (*e.g.*, tranilast[2]) depends on inhibition of mediator release. Other drugs (*e.g.*, oxatomide,[3] azelastin[4] and ketotifen[5]) possess antagonist activities against chemical mediators such as histamine, serotonin and slow-reacting substance of anaphylaxis (leukotrienes). Recently, the leukotrienes (LTC_4, LTD_4 and LTE_4) have been noted as important mediators of allergic reactions.[6] Inhibitors of the enzyme 5-lipoxygenase, which catalyzes the generation of the leukotrienes from arachidonic acid, may be useful candidate drugs for treating allergic diseases. However, there is no currently available drug having 5-lipoxygenase inhibitory activity. Compounds exhibiting several of the biological activities described above are expected to be more efficacious against asthma and other allergic diseases since various chemical mediators are considered to be involved. The present study was undertaken to find orally potent antiallergic compounds with inhibitory activities against the release of chemical mediators and 5-lipoxygenase, as well as antihistamine activity.

Compounds were designed, which are expected to possess both mediator-release-inhibitory and antihistamine activities. Reviewing the structural features of DSCG, amoxanox[7] and Sm-857[8] with inhibitory activity against chemical mediator release, we thought that the frameworks shown by the bold lines in Chart 1 would be essential for the activity; hence, β-aryl- and β-heteroarylacrylic acid structures (**1**) could be drawn from these frameworks. Tranilast contains a β-phenylacrylamide moiety instead of a β-arylacrylic acid, that is a β-phenylacrylic acid, and the acrylamide moiety may contribute to mediator-release-inhibitory activity. β-Aryl- and β-heteroarylacrylamides may also show the activity. Consequently, we designed the acrylamide derivatives (**2**), substituted with a 4-diphenylmethyl-1-piperazinylalkyl group, which, on the other hand, is expected to possess antihistamine activity similarly to oxatomide. To test these assumptions, a new series of β-aryl- and β-heteroarylacrylamides were prepared and evaluated for antiallergic activity. Some of the β-aryl- and β-heteroarylacrylamides prepared were found to possess potent inhibitory activity against the rat passive cutaneous anaphylaxis (PCA) reaction by oral administration. In addition, compound **10d**, which was the most potent inhibitor of the PCA reaction among the compounds prepared in the present study, proved to have more potent inhibitory activity than caffeic acid[9] against 5-

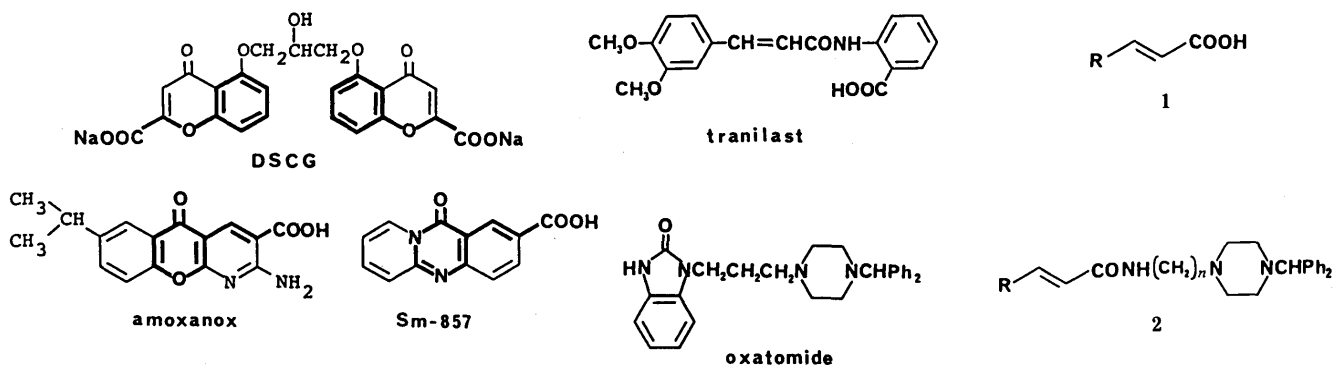
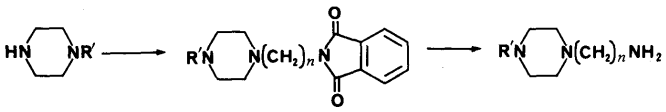


Chart 1

lipoxygenase. Further biological evaluation revealed that compound **10d** has antiallergic properties such as inhibitory activity against chemical mediator release and antihistamine activity, as well as inhibitory activity against 5-lipoxygenase.

Chemistry

The requisite amines (**5a—e** and **6c**) listed in Table I were synthesized from 1-diphenylmethylpiperazine and 1-(4-fluorophenyl)piperazine which were converted to the phthalimides (**3a—e** and **4c**, respectively), followed by cleavage of the phthalimido group with hydrazine (Chart 2). The acrylamides (**7—10**) listed in Tables II—IV were prepared from the corresponding acrylic acids (**1**) and the appropriate amines by (i) the acid chloride method (procedure A), (ii) the mixed anhydride method (procedure B), and (iii) the *N*,*N*′-dicyclohexylcarbodiimide (DCC) method (procedure C) (Chart 3). The acrylamides (**7—10**) were assigned *E*-configuration on the basis of the coupling constants of the olefinic protons ($J = 16$ Hz) in the proton nuclear magnetic resonance (^{1}H-NMR) spectra.



3a—e: R′=CHPh$_2$ **5a—e**: R′=CHPh$_2$
4c: R′=4-FPh **6c**: R′=4-FPh

For the **a** series, $n=2$; **b**, $n=3$; **c**, $n=4$; **d**, $n=5$; **e**, $n=6$

Chart 2

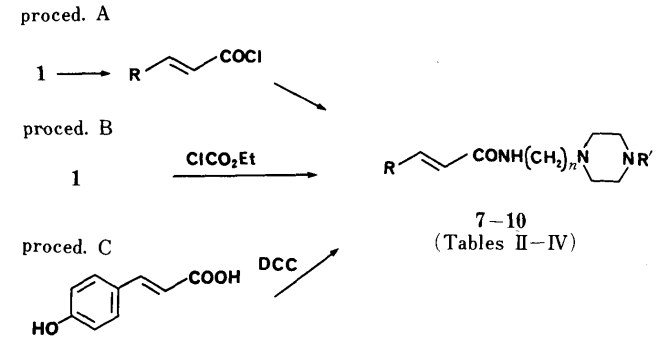


Chart 3

Physical data for compounds **5**, **6** and **7—10** are given in Tables I—IV.

Pharmacological Results

The compounds described were tested in the rat PCA assay by oral administration 1 h before antigenic challenge and their structure–activity relationships (SARs) were examined.

We focused our initial effort on the SARs associated with the methylene chain length in the cinnamamides (**7a—e**). As given in Table II, the four-carbon separation (**7c**) between the two nitrogen atoms in the aminoalkylpiperazine moiety was optimum; the activity was weaker when the methylene chain length was either shorter or longer.

Compounds **8a—d** with substituents (R′) other than the diphenylmethyl group, showed weaker PCA-inhibitory activity than **7c** (Table II). Therefore, the diphenylmethyl group was selected as the optimum substituent at the 4-position of the piperazinyl group.

Next, the effect of substitution on the benzene ring of the cinnamoyl moiety was examined (Table III). The introduction of a halogen, such as fluoro (**9a**) or chloro (**9b**), a methoxy (**9c**) and a hydroxy (**9d**) group into the *para* position of the benzene ring caused an increase in activity in comparison with the unsubstituted congener (**7c**). The order of activity with the various *para*-substituents was OH > F > OMe > Cl > Ph. Compound **9d** with a hydroxy group was the most active among the cinnamamides (**7—9**). On the other hand, the introduction of the same substituents (**9f** and **9h**) as well as trifluoromethyl (**9g**) and phenoxy groups (**9i**) into the *meta* position resulted in a decrease in activity.

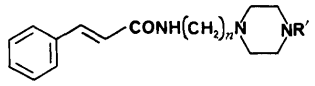
The effect of the replacement of the benzene ring by other aromatic and heteroaromatic rings is given in Table IV. The replacement of the benzene ring of **7c** by the naphthalene ring (**10a** and **10b**) did not cause a marked increase in activity. The furyl (**10f**), thienyl (**10g**) and quinolyl (**10h—j**) derivatives showed inhibitory activity comparable to that of the parent compound (**7c**). On the other hand, the replacement of the benzene ring of **7c** by the pyridine ring (**10c—e**) caused an increase in activity; in particular, the replacement by the 3-pyridyl group (**10d**) caused a marked increase in

TABLE I. 1-Aminoalkyl-4-diphenylmethyl- and 1-Aminoalkyl-4-(4-fluorophenyl)piperazines

Compd.	R′	*n*	Salt	mp (°C) (Recryst. solvent)	Yield[a] (%)	Formula	Analysis (%) Calcd (Found)			
							C	H	F	N
5a	$CHPh_2$	2	2 Fumarate	184—186 (EtOH)	38	$C_{19}H_{25}N_3 \cdot 2C_4H_4O_4$	61.47 (61.24	6.31 6.45		7.96 7.95)
5b	$CHPh_2$	3	3/2 Fumarate	197—199 (EtOH)	61	$C_{20}H_{27}N_3 \cdot 3/2\,C_4H_4O_4$	64.58 (64.66	6.88 7.08		8.69 8.69)
5c	$CHPh_2$	4	3 Maleate	159—162 (EtOH)	65	$C_{21}H_{29}N_3 \cdot 3C_4H_4O_4$	59.01 (58.84	6.15 6.13		6.25 6.30)
5d	$CHPh_2$	5	2 Fumarate	119—122 (EtOH)	46	$C_{22}H_{31}N_3 \cdot 2C_4H_4O_4$	63.03 (62.98	7.23 7.16		7.35 7.45)
5e	$CHPh_2$	6	2 Fumarate	139—142 (EtOH)	51	$C_{23}H_{33}N_3 \cdot 2C_4H_4O_4 \cdot H_2O$	61.88 (62.16	7.20 7.36		6.98 7.28)
6c	4-FPh	4	2 Oxalate	200—203 (EtOH)	93	$C_{14}H_{22}FN_3 \cdot 2C_2H_2O_4$	50.11 (50.17	6.07 6.12	4.40 4.67	9.74 9.67)

a) Total yields (%) of the free bases based on the corresponding piperazines.

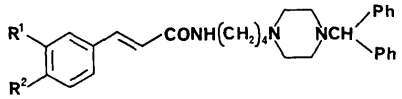
TABLE II. *N*-[(4-Substituted 1-Piperazinyl)alkyl]cinnamamides



Compd.	*n*	R′	Procedure[a]	mp (°C) (Recryst. solvent[b])	Formula	Yield (%)	Analysis (%) Calcd (Found) C	H	F	N	Rat PCA test Inhibition, % (mg/kg, *p.o.*)
7a[c]	2	$CHPh_2$	A	[d]	$C_{28}H_{31}N_3O \cdot 2C_4H_4O_4$	85[e]	425.528[f] (425.2478)				35.6[g] (80)
7b[c]	3	$CHPh_2$	A	163—165 (A)	$C_{29}H_{33}N_3O \cdot 2C_4H_4O_4$	61	66.16 (66.10	6.15 6.00		6.26 6.32)	42.2[g] (80)
7c	4	$CHPh_2$	A	153—155 (B)	$C_{30}H_{35}N_3O$	61	79.43 (79.71	7.78 7.97		9.26 9.35)	75.2[g] (80) 26.8[g] (20)
7d[h]	5	$CHPh_2$	A	116—118 (A)	$C_{31}H_{37}N_3O \cdot 2C_4H_6O_6 \cdot 2H_2O$	54	58.27 (58.32	6.65 6.35		5.23 5.13)	16.9 (20)
7e[h]	6	$CHPh_2$	A	103—105 (C)	$C_{32}H_{39}N_3O \cdot 2C_4H_6O_6 \cdot 1/2\,H_2O$	65	66.47 (66.24	6.69 6.65		5.81 5.83)	9.3 (20)
8a	4	Ph	A	163—165 (C)	$C_{23}H_{29}N_3O$	82	76.00 (76.11	8.04 8.19		11.56 11.34)	15.1 (80)
8b	4	4-FPh	A	177—179 (D)	$C_{23}H_{28}FN_3O \cdot 1/4\,H_2O$	50	71.59 (71.59	7.44 7.71	4.92 5.21	10.89 10.76)	33.3[g] (80)
8c	4	2-pyridyl	A	104—105 (A)	$C_{22}H_{28}N_4O$	53	72.50 (72.48	7.74 7.82		15.37 15.28)	53.4[g] (80)
8d	4	CH_2Ph	A	91—93 (E)	$C_{24}H_{31}N_3O \cdot 1/4\,H_2O$	50	75.45 (75.22	8.31 8.35		11.00 10.97)	4.5 (20)

a) Capital letters refer to the procedures in Experimental. *b*) Abbreviations for the solvent used are as follows: A, EtOH–Et_2O; B, EtOH–hexane; C, EtOH; D, iso-PrOH; E, iso-PrOH–hexane; F, iso-PrOH–Et_2O; G, MeOH; H, EtOH–iso-PrOH; I, toluene–hexane; J, MeOH–iso-PrOH; K, toluene. *c*) Dimaleate. *d*) Isolated as a white foam. *e*) Crude yield after partial chromatographic purification; $CHCl_3$–MeOH (30 : 1) on SiO_2. *f*) Determined by high-resolution mass spectrometry. Upper figure, calcd for M^+ and lower figure, found. *g*) $p<0.01$, significant difference between means. *h*) Ditartrate.

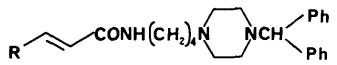
TABLE III. *N*-[4-(4-Diphenylmethyl-1-piperazinyl)butyl]-3-(substituted phenyl)acrylamides



Compd.	R^1	R^2	Procedure[a]	mp (°C) (Recryst. solvent[b])	Formula	Yield (%)	Analysis (%) Calcd (Found) C	H	Halogen	N	Rat PCA test Inhibition, % 20 mg/kg, *p.o.*
9a	H	F	A	155—157 (D)	$C_{30}H_{34}FN_3O$	45	69.09 (68.87	7.12 7.26	4.97 4.86	14.65 14.59)	47.5[c]
9b	H	Cl	A	140—141 (E)	$C_{30}H_{34}ClN_3O \cdot 3/4\,H_2O$	35	71.84 (71.87	7.14 6.98	7.02 7.22	8.38 8.27)	30.7[c]
9c	H	OMe	A	120—124 (F)	$C_{31}H_{37}N_3O_2 \cdot 1/2\,H_2O$	20	75.58 (75.30	7.77 7.73		8.53 8.35)	37.8[c]
9d[d]	H	OH	C	204—208 (G)	$C_{30}H_{35}N_3O_2 \cdot C_4H_4O_4$	16	69.72 (69.70	6.71 6.81		7.17 7.20)	57.8[e]
9e	H	Ph	A	147—148 (G)	$C_{36}H_{39}N_3O$	63	81.63 (81.48	7.42 7.58		7.93 7.87)	17.0[e]
9f	F	H	A	139—141 (D)	$C_{30}H_{34}FN_3O$	71	76.40 (76.46	7.27 7.37	40.3 3.86	8.91 8.91)	18.6[e]
9g[f]	CF_3	H	A	167—169 (E)	$C_{31}H_{34}F_3N_3O \cdot 2C_2H_2O_4$	44	59.91 (59.82	5.46 5.60	8.12 8.22	5.99 6.07)	13.7
9h[f]	OH	H	B	105—109 (D)	$C_{30}H_{35}N_3O_2 \cdot 2C_2H_2O_4 \cdot 3/2\,H_2O$	35	60.35 (60.55	6.26 6.19		6.21 6.03)	12.9
9i	OPh	H	A	122—124 (E)	$C_{36}H_{39}N_3O_2$	60	79.23 (79.08	7.20 7.46		7.70 7.57)	28.0[c]
9j[f]	Cl	Cl	A	112—113 (H)	$C_{30}H_{33}Cl_2N_3O \cdot 2C_2H_2O_4 \cdot 1/4\,H_2O$	58	57.75 (57.78	5.35 5.46	10.03 10.08	5.94 5.93)	1.6
9k[g]	OMe	OMe	A	[h]	$C_{32}H_{39}N_3O \cdot 2C_4H_6O_6$	35[i]	513.632[j] (513.3013)				17.8

a) See footnote *a*) in Table II. *b*) See footnote *b*) in Table II. *c*) $0.01<p<0.05$. *d*) Maleate. *e*) $p<0.01$. *f*) Dioxalate. *g*) Ditartrate. *h*) Isolated as a white foam. *i*) See footnote *e*) in Table II. *j*) See footnote *f*) in Table II.

TABLE IV. *N*-[4-(4-Diphenylmethyl-1-piperazinyl)butyl]-3-(aryl and heteroaryl)acrylamides



Compd.	R	Procedure[a]	mp (°C) (Recryst. solvent[b])	Formula	Yield (%)	Analysis (%) Calcd (Found) C	H	N	S	Rat PCA test Inhibition, % 20 mg/kg, *p.o.*
10a	1-Naphthyl	A	136—138 (D)	$C_{34}H_{37}N_3O$	42	81.08 (81.15	7.40 7.59	8.34 8.35)		43.5[c]
10b	2-Naphthyl	A	161—163 (D)	$C_{34}H_{37}N_3O$	60	81.08 (81.04	7.40 7.34	8.34 8.34)		33.6[d]
10c	2-Pyridyl	B	140—142 (E)	$C_{29}H_{34}N_4O \cdot 1/4\,H_2O$	45	75.87 (76.06	7.57 7.80	12.20 12.08)		46.3[c]
10d	3-Pyridyl	A	144—146 (I)	$C_{29}H_{34}N_4O$	60	76.62 (76.67	7.54 7.77	12.32 12.12)		62.3[c]
10e[e]	4-Pyridyl	A	110—112 (J)	$C_{29}H_{34}N_4O \cdot 3C_2H_2O_4 \cdot 3/2\,H_2O$	16	55.92 (55.89	5.77 5.72	7.45 7.17)		46.3[d]
10f	2-Furyl	A	120—122 (K)	$C_{28}H_{33}N_3O_2$	45	75.81 (75.78	7.50 7.75	9.47 9.36)		26.2
10g	2-Thienyl	A	143—144.5 (I)	$C_{28}H_{33}N_3OS$	30	73.17 (73.05	7.24 7.40	9.14 9.02	6.98 7.00)	20.7[d]
10h	2-Quinolyl	A	169—171.5 (K)	$C_{33}H_{36}N_4O$	31	78.54 (78.30	7.19 7.07	11.10 11.11)		38.1[d]
10i	3-Quinolyl	B	185—187 (D)	$C_{33}H_{36}N_4O$	50	78.54 (78.38	7.19 7.34	11.10 10.96)		28.7[d]
10j	4-Quinolyl	B	161—162 (D)	$C_{33}H_{36}N_4O$	49	78.54 (78.78	7.19 7.29	11.10 10.97)		27.2[d]

a) See footnote *a*) in Table II. *b*) See footnote *b*) in Table II. *c*) $p<0.01$. *d*) $0.05<p<0.01$. *e*) Trioxalate.

TABLE V. Comparative Pharmacological Data for Compound **10d** and Reference Drugs

Compd.	Rat PCA test Inhibition, % 20 mg/kg, *p.o.*	Anti-hist.[a] IC_{50} (M) G.P.[b] trachea	Hist. release Inhibition, % (M) Rat mast cell	5-Lipoxygenase Inhibition, % (M) G.P. leukocyte
10d	62.3[c]	9.6×10^{-7}	36.3[c] (1×10^{-5})	46.0[c] (3×10^{-5})
Ketotifen	54.6[c]	2.9×10^{-9}	1.1 (1×10^{-5})	11.5 (1×10^{-4})
Tranilast	11.3[d]	$>1\times10^{-5}$	27.1[c] (3×10^{-5})	NT[f]
DSCG	71.8[c,e]	NT	53.7[c] (1×10^{-5})	NT
Caffeic acid	NT	NT	NT	22.7[c] (3×10^{-5})

a) hist.: histamine. *b*) G.P.: quinea pig. *c*) $p<0.01$, significant difference between means. *d*) Dose of 80 mg/kg, *p.o.* *e*) Dose of 1 mg/kg, i.v. *f*) NT: not tested.

activity. Compound **10d** was the most active in the rat PCA assay among the compounds prepared in the present study.[10]

Compound **10d** was further tested for inhibition of 5-lipoxygenase and mediator release, and *in vitro* antihistamine activity. The results from these tests are summarized in Table V, which includes the data for other antiallergic drugs for reference. Compound **10d** is equivalent or superior to ketotifen in activity on the rat PCA assay by oral administration. Unlike ketotifen, **10d** has more potent *in vitro* 5-lipoxygenase inhibitory activity than caffeic acid,[9] whereas its *in vitro* antihistamine activity is weaker than that of ketotifen. In addition, the *in vitro* histamine-release-inhibitory activity of **10d** is about two-thirds as potent as that of DSCG but higher than that of tranilast.

As a result of the present study, compound **10d**, possessing these three kinds of antiallergic activities, is considered to be a promising agent for treating a variety of allergic diseases.

Experimental

All melting points were determined on a Yanagimoto micromelting point apparatus, and are uncorrected. ^{1}H-NMR spectra were taken at 80 MHz with a Varian FT-80A spectrometer. Chemical shifts are expressed in δ (ppm) values with tetramethylsilane as an internal standard. Abbreviations are as follows: s, singlet; d, doublet. Electron impact mass spectra (EIMS) were recorded on a JEOL JMS D-300 or a Hitachi RMU-6L spectrometer. Organic extracts were dried over anhydrous $MgSO_4$.

The following known intermediates were prepared according to the cited methods: 4-fluoro-,[11] 4-chloro-,[11] 4-methoxy-,[12] 4-hydroxy-,[12] 4-phenyl-,[13] 3-fluoro-,[11] 3-trifluoromethyl-,[14] 3-hydroxy-,[12] 3-phenoxy-,[15] 3,4-dichloro-[12] and 3,4-dimethoxycinnamic acids[16]; 3-(1-naphthyl)-,[17] 3-(2-naphthyl)-,[18] 3-(2-pyridyl)-,[19] 3-(3-pyridyl)-,[19] 3-(4-pyridyl)-,[19] 3-(2-furyl)-,[20] 3-(2-thienyl)-,[21] 3-(2-quinolyl)-,[22] 3-(3-quinolyl)-[21] and 3-(4-quinolyl)acrylic acids[23]; 1-(4-aminobutyl)-4-phenyl-,[24] 1-(4-aminobutyl)-4-(2-pyridyl)-[25] and 1-(4-aminobutyl)-4-benzylpiperazines.[26]

1-(4-Aminobutyl)-4-diphenylmethylpiperazine (5c) A mixture of *N*-(4-bromobutyl)phthalimide[27] (67 g, 0.24 mol), 1-diphenylmethylpiperazine (60 g, 0.24 mol), K_2CO_3 (49.3 g, 0.36 mol), NaI (49.9 g, 0.33 mol) and methyl ethyl ketone (1.2 l) was heated at reflux temperature for 4.5 h with stirring. After the mixture had cooled, the insoluble materials were removed by filtration and washed with $CHCl_3$. The filtrate and the washings were concentrated to dryness *in vacuo*. The residue was taken up in 800 ml of $CHCl_3$. The $CHCl_3$ layer was washed with water, dried, and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel with $CHCl_3$ as an eluent. The product obtained from the main fraction was recrystallized from acetonitrile to give *N*-(4-diphenylmethyl-1-piperazinylbutyl)phthalimide (**3c**) (80.0 g, 74%), mp

122—124 °C. A solution of **3c** (60 g, 0.13 mol) and hydrazine hydrate (13.0 g, 0.26 mol) in ethanol (EtOH) (420 ml) was refluxed for 2 h with stirring. After the solution had cooled, the insoluble materials were removed by filtration and washed with EtOH. The filtrate and the washings were concentrated to dryness *in vacuo*. The residue was taken up in 600 ml of toluene. The toluene layer was washed twice with water (40 ml), dried, and concentrated to give crude **5c** (37.6 g, 88%). The crude **5c**, without further purification, was used for the preparation of the corresponding acrylamides (**7c**, **9a—k** and **10a—j**). The trimaleate of **5c**, mp 159—162 °C, was subjected to elemental analysis (Table I).

4-Substituted 1-(Aminoalkyl)piperazines (5a, 5b, 5d, 5e and 6c) 1-(2-Aminoethyl)- (**5a**), 1-(3-aminopropyl)- (**5b**), 1-(5-aminopentyl)- (**5d**) and 1-(6-aminohexyl)-4-diphenylmethylpiperazines (**5e**), and 1-(4-aminobutyl)-4-(4-fluorophenyl)piperazine (**6c**) were prepared from *N*-(2-bromoethyl)-, *N*-(3-bromopropyl)-, *N*-(5-bromopentyl)-,[28] *N*-(6-bromohexyl)-[28] and *N*-(4-bromobutyl)phthalimides, respectively, in a manner similar to that described for **5c** (Table I).

Acrylamides 7—10 (Tables II—IV). Procedure A. *N*-[4-(4-Diphenylmethyl-1-piperazinyl)butyl]-3-(4-fluorophenyl)acrylamide (9a) Sodium 4-fluorocinnamate[11] (1.2 g, 6.3 mmol) was added portionwise to a stirred solution of oxalyl chloride (1.2 g, 9.4 mmol) in toluene (50 ml) at room temperature. The mixture was stirred at 80 °C for 1.5 h and then cooled to room temperature. The insoluble materials were removed by filtration and the filtrate was concentrated to dryness to give 4-fluorocinnamoyl chloride (1.3 g, 90%). This product was dissolved in 10 ml of toluene, 2.1 g (6.5 mmol) of **5c** was added, and the mixture was stirred overnight at room temperature. Then 50 ml of 10% K_2CO_3 was added and the mixture was extracted with two 100-ml portions of $CHCl_3$. The combined extracts were dried and the solvent was removed by distillation *in vacuo*. The residue was crystallized from 2-propanol (iso-PrOH) to give **9a** (1.4 g, 50%). EIMS *m/z*: 471 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 4.23 (1H, s, $-CHPh_2$), 6.55 (1H, d, J=16 Hz, $-CH=CHCO-$) (Table III).

Procedure B. *N*-[4-(4-Diphenylmethyl-1-piperazinyl)butyl]-3-(3-quinolyl)acrylamide (10i) A solution of triethylamine (0.63 g, 6.2 mmol) in anhydrous tetrahydrofuran (THF) (1.5 ml) was added to a suspension of 3-(3-quinolyl)acrylic acid[21] (1.20 g, 6.0 mmol) in anhydrous THF (27 ml) at room temperature. The resulting solution was cooled to −10—−5 °C, and a solution of ethyl chlorocarbonate (0.67 g, 6.2 mmol) in anhydrous THF (1.5 ml) was added slowly. The mixture was stirred at the same temperature for 2 h, then a solution of 1.2 g of **5c** in anhydrous THF (2.5 ml) was added. The mixture was stirred for 1 h at −10—−5 °C and then at room temperature overnight. The insoluble materials were removed by filtration and the filtrate was concentrated to dryness. The residue was recrystallized from iso-PrOH to give **10i** (1.46 g, 50%). EIMS *m/z*: 504 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 4.10 (1H, s, $-CHPh_2$), 6.59 (1H, d, J=16 Hz, $-CH=CHCO-$) (Table IV).

Procedure C. *N*-[4-(4-Diphenylmethyl-1-piperazinyl)butyl]-3-(4-hydroxyphenyl)acrylamide Maleate (9d) A mixture of 4-hydroxycinnamic acid[12] (1.02 g, 6.2 mmol), **5c** (2.0 g, 6.2 mmol), DCC (1.27 g, 6.2 mmol) and 1,4-dioxane (40 ml) was stirred at room temperature for 2 d. The insoluble materials were removed by filtration and the filtrate was concentrated to dryness *in vacuo*. The residue was taken up in $CHCl_3$ (50 ml). The resulting solution was washed with water, dried, and concentrated to dryness *in vacuo*. The residue was subjected to column chromatography on silica gel with $CHCl_3$–methanol (MeOH) (50 : 1) as an eluent. Treatment of the oily product obtained from the main fraction with a solution of 1.4 g of maleic acid in MeOH gave **9d** (0.8 g, 16%). EIMS *m/z*: 469 (M^+). ^{1}H-NMR ($(CH_3)_2SO$-d_6) δ: 4.47 (1H, s, $-CHPh_2$), 6.36 (1H, d, J=16 Hz, $-CH=CHCO-$) (Table III).

Pharmacological Methods

Rat Passive Cutaneous Anaphylaxis (PCA) Assay[29] Male Std: Wistar rats (140—200 g) were injected with 0.1 ml of a dilute solution of mouse antiserum to egg albumin in two sites of the shaved ventral skin. Forty-eight hours later, each rat was challenged by an intravenous injection of 2 mg of the antigen together with 1 ml of a 0.5% Evan's blue saline solution. The rats were sacrificed 30 min after the challenge. The dimensions (shortest × longest diameters) of the blueing lesions were measured on the undersurface of the skin. Test compounds were dissolved or suspended in a 0.5% gum tragacanth aqueous solution and administered orally to the rats 1 h before antigen challenge. The antiallergic activity of the compounds was expressed as percent inhibition of the dimensions compared with the control group. Mouse anti-egg albumin antiserum was produced by the method of Levine and Vaz.

Antihistamine Assay Zig-zag strips of guinea pig trachea were prepared by the method of Emmerson and Mackay.[30] Dose-response curves for histamine were obtained before and 5 min after the addition of test compounds. Inhibitory rate was calculated from contraction heights in 3×10^{-5} M histamine without *vs.* with a test compound. IC_{50} values were determined from the best fit linear regression line of the inhibitory rates of histamine response.

Histamine Release Assay[31] Male Wistar rats (150—300 g) were sensitized passively by an intraperitoneal administration of rat anti-serum to egg albumin. About 20 h later rats were sacrificed by bleeding. Peritoneal exudate cells (PEC) were collected by injection of 10 ml of Hank's balanced salt solution (Hank's BSS) containing 1 mg/ml of human albumin and 2 units/ml of heparin into the abdominal cavity. Histamine release was expressed as a percentage of the supernatant histamine with respect to the total histamine. The effect of test compounds was calculated from release rates of histamine without *vs.* with a test compound.

5-Lipoxygenase Assay The test was carried out according to the method of Ochi *et al.*,[32] and Miyamoto and Obata[33] with minor modifications. In brief, the cytosol fraction of peritoneal exudate cells of guinea pigs was used as 5-lipoxygenase. The reaction mixture was incubated for 5 min at 30 °C after addition of [1-^{14}C]arachidonic acid (0.02 μCi). 5-Lipoxygenase activity was expressed as the conversion rate of arachidonic acid to 5-hydroxy-6,8,11,14-eicosatetraenoic acid (5-HETE) in 5 min. The effect of test compounds was expressed as percent inhibition of the conversion rate compared with the control.

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