Acrylamide Derivatives as Antiallergic Agents. III.[1,2] Synthesis and Structure–Activity Relationships of *N*-[4-(4-Diphenylmethyl-1-piperazinyl)butyl]- and *N*-[4-(4-Diphenylmethylene-1-piperidyl)butyl]-3-heteroarylacrylamides

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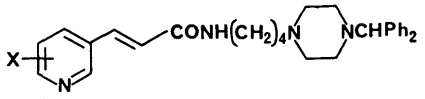
A new series of 3-heteroarylacrylamides 2 and 4 was prepared and the inhibitory activities against the rat passive cutaneous anaphylaxis (PCA) reaction and the enzyme 5-lipoxygenase (5-LO) were tested. Most of the compounds exhibited an anti-PCA activity superior to or equivalent to ketotifen and had a 5-LO inhibitory activity. The 3-heteroarylacrylamide derivatives including 3-(3-pyridyl)acrylamides represent a new structural class of compound that exhibits not only an *in vivo* anti-PCA activity but also an *in vitro* 5-LO inhibitory activity.

Keywords *N*-[4-(4-diphenylmethyl-1-piperazinyl)butyl]-3-heteroarylacrylamide; *N*-[4-(4-diphenylmethylene-1-piperidyl)-butyl]-3-heteroarylacrylamide; antiallergic agent; anti-PCA activity; 5-lipoxygenase inhibitory activity

We recently reported[1,2] that *N*-[4-(4-diphenylmethyl-1-piperazinyl)butyl]-3-(3-pyridyl)acrylamides (**1**) (Chart 1) displayed an inhibitory activity against the rat passive cutaneous anaphylaxis (PCA) reaction by oral administration. In particular, (*E*)-*N*-[4-(4-diphenylmethyl-1-piperazinyl)butyl]-3-(6-methyl-3-pyridyl)acrylamide (**1b**) (AL-3264) was 5 times as potent as ketotifen[3] in its anti-PCA activity, and was characterized as an antagonist of histamine as well as an inhibitor of the enzyme 5-lipoxygenase (5-LO) catalyzing the generation of leukotrienes (LTA_4, LTB_4, LTC_4, LTD_4 and LTE_4) from arachidonic acid and histamine release from healthy human basophils induced by anti-human immunoglobulin E (IgE) antibody.



1
1a: X=H
1b: X=6-Me

Chart 1

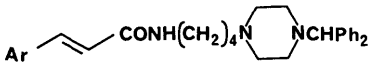


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Chart 2

From the earlier finding[1] that the acrylamide derivatives with phenyl, furyl, thienyl and quinolyl groups as Ar in Chart 2 showed a weaker anti-PCA activity than the pyridyl derivative **1a**, we assumed the activity of **2** to be influenced by the hydrophilicity of the substituents (Ar); the log *P* value of pyridine is smaller than those of benzene, furan, thiophene and quinoline.[4] To confirm this, a new series of 3-heteroarylacrylamides, substituted with various heteroaryl groups containing nitrogen atom(s), were prepared without changing the 4-(4-diphenylmethyl-1-piperazinyl)butyl moiety; this moiety seems to be an important constituent for the antihistamine activity, since 1-(*p*-chloro-α-phenylbenzyl)-4-methylpiperazine (chlorcyclizine)[5] exhibits the activity. The anti-PCA activity of these compounds was then evaluated. In addition, their *in vitro* 5-LO inhibitory activity was tested, since we were interested in determining whether or not they had a 5-LO inhibitory activity similarly to **1a** and **1b**.

Chemistry The requisite 3-heteroarylacrylic acids **3a**—**f**, **3h** and **3j** were synthesized by the routes shown in Chart 3. Thus, compounds **3a**, **3b** and **3d** were prepared by condensation of the respective methyl derivatives with chloral according to known procedures.[6,7] Compound **3c** was prepared by starting with 5-bromopyrimidine and employing a method analogous to that of Sakamoto *et al.*[8] Compounds **3e**,[9] **3f** and **3h** were prepared by means of the Wittig–Horner reaction starting with the corresponding aldehydes.[10,11] Compound **3j** was prepared by condensation of the corresponding aldehyde[12] with malonic acid in a manner similar to the method given in the literature.[13] 3-(4-Imidazolyl)acrylic acid (**3g**) and 3-(3-indolyl)acrylic acid (**3i**) were obtained commercially.

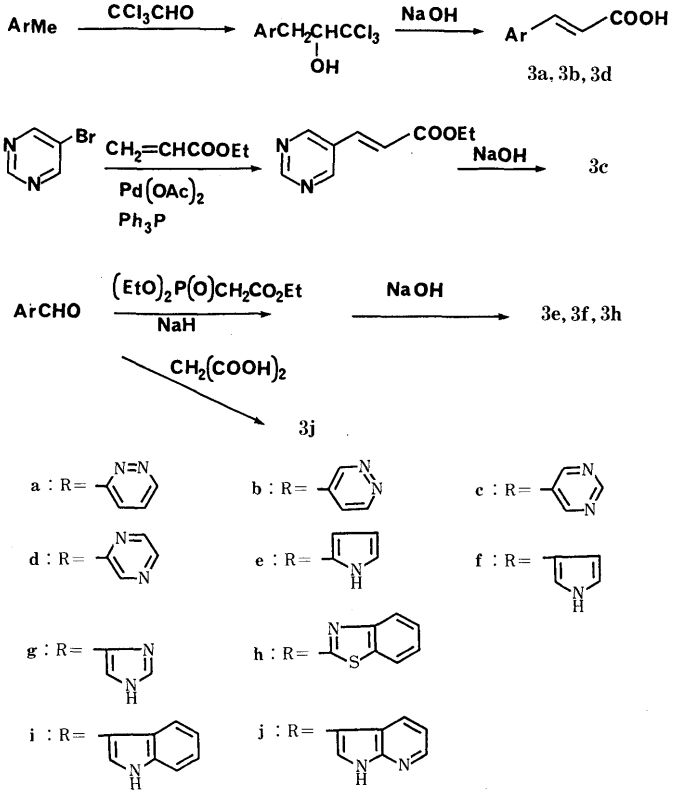

Chart 3

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The acrylic acids **3a**—**f**, **3h** and **3i** were condensed with 1-(4-aminobutyl)-4-diphenylmethylpiperazine (**8**) or 1-(4-aminobutyl)-4-diphenylmethylenepiperidine (**9**)[14] by the use of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (procedure A) (Chart 4), giving the desired acrylamides **2a**—**f**, **2h**, **2i**, **4a**, **4c** and **4d** (Table I). Attempts to condense **3g** and **3j** with **8** by the use of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride and ethyl chlorocarbonate were unsuccessful. Compounds **2g** and **2j** were prepared by using *p*-nitrophenyl trifluoroacetate (procedure B) and *N*,*N*′-dicyclohexylcarbodiimide (DCC) (procedure C), respectively. The acrylamides **2** and **4** so prepared were assigned the *E*-configuration on the basis of the coupling constants for the olefinic protons ($J=16$ Hz) in their proton nuclear magnetic resonance (^{1}H-NMR) spectra.

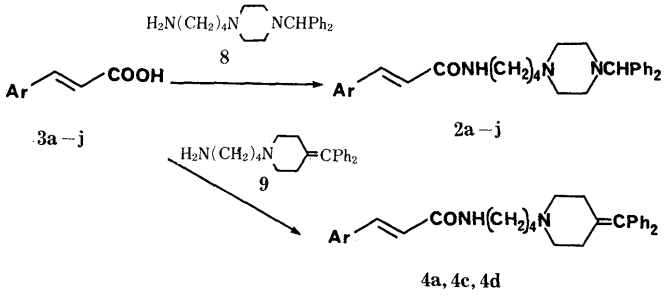
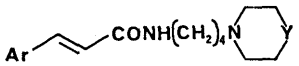


Chart 4

Pharmacological Results Compounds **2** and **4** were first evaluated for their antiallergic activity in the rat PCA test by oral administration 1 h before antigenic challenge.[1] The results are summarized in Table II. The 6-membered heteroaryl derivatives with pyridazinyl (**2a** and **2b**), pyrimidinyl (**2c**) and pyrazinyl groups (**2d**) containing two nitrogen atoms and the 5-membered heteroaryl derivatives **2e** and **2f** with a pyrrolyl group containing one nitrogen atom, exhibited a potent inhibitory activity against the PCA reaction similarly to **1a** and **1b**. Among compounds **2** and **4**, compound **2a** was the most potent inhibitor, showing an inhibitory rate of 92.1% at 20 mg/kg (*p.o.*). However, compound **2g** with the 5-membered heteroaryl group containing two nitrogen atoms, *i.e.* the imidazolyl group, had a reduced activity. The bicyclic compounds **2i** and **2j** with indolyl and 7-azaindolyl groups, respectively, were substantially less active than the pyrrolyl derivative **2f**, similarly to the relationship between the quinolyl derivative **6**[1] and the pyridyl derivative **1a**. As a result, the acrylamide derivatives having more hydrophilic groups such as pyrrolyl (**2e** and **2f**), pyrazinyl (**2d**), pyrimidinyl (**2c**) and pyridazinyl (**2a** and **2b**), except the imidazolyl derivative **2g**,

TABLE I. 3-(Heteroaryl)acrylamides



Compd.	Ar	Y	Procedure[a]	mp (°C) (Recryst. solvent[b])	Yield (%)	Formula	Analysis (%) Calcd (Found)			
							C	H	N	S
2a	3-Pyridazinyl	$NCHPh_2$	A	186—188 (A)	35	$C_{28}H_{33}N_5O\cdot 1/4\,H_2O$	73.09 (73.25)	7.34 7.07	15.22 15.02)	
2b	4-Pyridazinyl	$NCHPh_2$	A	79—83 c)	25	$C_{28}H_{33}N_5O\cdot 1/4\,H_2O$	73.09 (73.34)	7.34 7.26	15.22 14.96)	
2c	5-Pyrimidinyl	$NCHPh_2$	A	126—128 (A)	28	$C_{28}H_{33}N_5O\cdot 1/4\,H_2O$	73.09 (73.25)	7.34 7.30	15.22 15.37)	
2d[d]	2-Pyrazinyl	$NCHPh_2$	A	198—202 (dec.) (B)	55	$C_{28}H_{33}N_5O\cdot 3/2\,C_4H_4O_4$	64.85 (65.14)	6.24 6.01	11.12 11.06)	
2e	2-Pyrrolyl	$NCHPh_2$	A	162—164 (A)	22	$C_{28}H_{34}N_4O\cdot 1/4\,H_2O$	75.22 (75.04)	7.78 8.08	12.53 12.42)	
2f[e]	3-Pyrrolyl	$NCHPh_2$	A	128—132 (C)	47	$C_{28}H_{34}N_4O\cdot C_4H_6O_6\cdot H_2O$	62.94 (63.17)	6.93 6.84	9.17 9.06)	
2g[f]	4-Imidazolyl	$NCHPh_2$	B	132—135 (B)	16	$C_{27}H_{33}N_5O\cdot 3/2\,C_4H_6O_6$	57.72 (57.40)	6.45 6.80	10.19 9.90)	
2h	2-Benzothiazolyl	$NCHPh_2$	A	166—168 (A)	38	$C_{31}H_{34}N_4OS$	72.91 (72.99)	6.71 6.81	10.97 10.80	6.28 6.18)
2i[g]	3-Indolyl	$NCHPh_2$	A	205—206 (D)	35	$C_{32}H_{36}N_4O\cdot C_4H_4O_4\cdot H_2O$	66.97 (67.13)	6.58 6.83	11.16 11.14)	
2j[g]	3-(7-Azaindolyl)	$NCHPh_2$	C	144—146 (E)	20	$C_{31}H_{35}N_5O\cdot C_4H_4O_4\cdot 2H_2O$	65.10 (65.31)	6.71 6.56	10.85 10.76)	
4a	3-Pyridazinyl	$C=CPh_2$	A	187—188 (B)	39	$C_{29}H_{32}N_4O$	76.96 (76.80)	7.13 7.43	12.38 12.09)	
4c	5-Pyrimidinyl	$C=CPh_2$	A	131—134 (A)	25	$C_{29}H_{32}N_4O$	76.96 (76.72)	7.13 7.22	12.38 12.13)	
4d	2-Pyrazinyl	$C=CPh_2$	A	130—131 (A)	34	$C_{29}H_{32}N_4O$	76.96 (76.90)	7.13 7.40	12.38 12.35)	
5[h]	2-Quinolyl	$NCHPh_2$								
6[h]	3-Quinolyl	$NCHPh_2$								
7[h]	4-Quinolyl	$NCHPh_2$								

a) Capital letters refer to the procedures described in Experimental. *b*) Abbreviations for the solvents used are as follows: A, acetonitrile; B, EtOH; C, EtOH–Et_2O; D, EtOH–MeOH; E, acetonitrile–EtOH. *c*) Washed with ether following purification by column chromatography. *d*) Sesquifumarate. *e*) Tartrate. *f*) Sesquitartrate. *g*) Fumarate. *h*) These compounds were previously prepared.[1]

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TABLE II. Inhibitory Activities against the Rat PCA Reaction and 5-Lipoxygenase

Compd.	Rat PCA test (Inhibition %, 20 mg/kg, *p.o.*)	5-Lipoxygenase (Inhibition %, at 10 μM)
1a	62.3[a]	2.3[b]
1b	81.9[a]	45.7[a]
2a	92.1[a]	20.7[b]
2b	54.8[a]	15.2[a]
2c	60.6[a]	46.1[a]
2d	54.2[a]	13.7[b]
2e	74.1[a]	63.6[a]
2f	40.8[a]	75.7[a]
2g	6.1[b]	39.9[b]
2h	33.6[b]	78.2[a]
2i	3.0[b]	—[c]
2j	11.8[b]	77.0[a]
4a	87.0[a]	36.2[a]
4c	77.1[a]	31.4[a]
4d	65.7[a]	40.8[a]
5[d]	38.1[a]	96.3[a]
6[d]	28.7[a]	76.7[a]
7[d]	27.2[a]	97.6[a]
Caffeic acid[e]	—[c]	22.7[a,f]
Ketotifen	54.6[a]	11.5[b,g]

a) $p<0.05$, significantly different from the matched vehicle control. *b*) Not statistically significant. *c*) Not tested. *d*) These compounds were previously evaluated for anti-PCA activity.[1] *e*) This compound has been reported as an inhibitor of 5-LO.[19] *f*) Inhibition % at 30 μM. *g*) Inhibition % at 100 μM.

exhibited a more potent anti-PCA activity when compared with the acrylamide derivatives having hydrophobic groups such as benzothiazolyl (**2h**), indolyl (**2i**) and 7-azaindolyl (**2j**).[4]

The 4-diphenylmethylene-1-piperidyl derivatives **4c** and **4d** displayed a higher activity in the PCA test than did the 4-diphenylmethyl-1-piperazinyl derivatives **2c** and **2d**. This coincided with earlier findings[2] on 3-(3-pyridyl)acrylamides. The activity of **4a**, however, was comparable to that of **2a**.

The *in vitro* 5-LO inhibitory activity of compounds **2** and **4** together with the quinolyl derivatives **5**, **6** and **7** prepared previously[1] was then tested by the assay method described previously[1] (Table II). Compound **2f** and the bicyclic compounds **2h**, **2j**, **5**, **6** and **7** exhibited a much more potent 5-LO inhibitory activity than **1b** (AL-3264), but were less active than **1b** in the PCA test. Compounds **2c**, **2e** and **4d** were potent inhibitors of 5-LO and the PCA reaction; compound **2e**, in particular, was more active than **1b** in its 5-LO inhibition, but somewhat weaker in its PCA inhibition. Compounds **2a**, **4a** and **4c**, which were superior to or equivalent to **1b** in their anti-PCA activity, were weaker than **1b** in their 5-LO inhibitory activity.

Structure–activity studies on the acrylamides **2** revealed that substitution of more hydrophilic groups such as pyrrolyl, pyridyl, pyrazinyl, pyrimidinyl and pyridazinyl groups at the β-position of the acryloyl moiety, caused an increase in anti-PCA activity when compared with the acrylamide derivatives having hydrophobic groups such as the phenyl, 3-quinolyl, 2-thienyl and 2-furyl derivatives (inhibitory rates of 26.8, 28.7, 20.7 and 26.2%, respectively, at 20 mg/kg, *p.o.*).[1] Similarly to the pyridine analogs **1a** and **1b** (Chart 1), most of the acrylamide derivatives **2** and **4**—**7** displayed a 5-LO inhibitory activity as well. These acrylamide derivatives **1a**, **1b**, **2** and **4**—**7** were all less active than the known antioxidants, nordihydroguaiaretic acid[15] and quercetin,[16] in their 5-LO inhibitory activity. These compounds, however, represent a new structural class of compounds that exhibit an *in vitro* 5-LO inhibitory activity as well as an *in vivo* anti-PCA activity.

Experimental

All melting points were determined on a Yanagimoto micromelting point apparatus, and are uncorrected. ^{1}H-NMR spectra were taken at 60 MHz with a Varian EM-360 spectrometer, at 80 MHz with a Varian FT-80A spectrometer or at 300 MHz with a Varian XL-300 spectrometer. Chemical shifts are expressed in δ (ppm) values with tetramethylsilane as the internal standard. The abbreviations used 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. Infrared (IR) spectra were recorded on a Hitachi 260-10 spectrometer using KBr disks. Organic extracts were dried over anhydrous $MgSO_4$.

The following known intermediates were prepared according to the cited literature: 3-pyrrole-,[10] 2-benzothiazole-[11] and 3-(7-azaindole)-carbaldehydes;[12] 3-(3-pyridazinyl)- (**3a**),[6] 3-(4-pyridazinyl)- (**3b**),[7] 3-(2-pyrazinyl)- (**3d**)[6] and 3-(2-pyrrolyl)acrylic acids (**3e**).[9]

(*E*)-3-(5-Pyrimidinyl)acrylic Acid (3c) A mixture of 5-bromopyrimidine (17.8 g, 0.11 mol), ethyl acrylate (14.6 g, 0.15 mol), $(CH_3CO_2)_2Pd$ (337 mg, 1.5 mmol), $(C_6H_5)_3P$ (674 mg, 2.6 mmol) and $(C_2H_5)_3N$ (13.6 g, 0.13 mol) was heated in a sealed tube at 150 °C for 6 h. The reaction mixture was diluted with 200 ml of water, made alkaline with K_2CO_3, and extracted with three 200-ml portions of toluene. The combined extracts were dried and concentrated to dryness *in vacuo* to give crude ethyl 3-(5-pyrimidinyl)acrylate (14.9 g, 75%).

A mixture of the crude acrylate (12.4 g, 0.070 mol), 2 N KOH (20 ml) and C_2H_5OH (40 ml) was heated at reflux temperature with stirring for 1 h. Ethanol was removed by distillation *in vacuo*. The aqueous solution was adjusted to pH 4 with 10% HCl. The resultant precipitate was collected, washed with water, and recrystallized from dimethylformamide (DMF) to give **3c** (6.0 g, 58%), mp > 300 °C (lit.[17] > 300 °C). EIMS *m/z*: 150 (M^+). ^{1}H-NMR (60 MHz, $(CH_3)_2SO$-d_6) δ: 6.85 (1H, d, J=16 Hz, –CH=CHCO–), 7.69 (1H, d, J=16 Hz, –CH=CHCO–), 9.23 (2H, s, aromatic proton), 9.26 (1H, s, aromatic proton). *Anal.* Calcd for $C_7H_6N_2O_2$: C, 56.00; H, 4.03; N, 18.66. Found: C, 55.88; H, 4.23; N, 18.56.

(*E*)-3-(3-Pyrrolyl)acrylic Acid (3f) To a solution of triethyl phosphonoacetate (2.6 g, 0.012 mol) in DMF (25 ml) were added slowly 0.46 g of NaH (about 60% in oil), and then 1.1 g (0.012 mol) of 3-pyrrolecarbaldehyde. The resultant mixture was stirred at room temperature overnight and concentrated *in vacuo*. The residue was taken up in 50 ml of water, and the aqueous mixture was extracted with three 50-ml portions of $CHCl_3$. The combined extracts were dried and concentrated to dryness *in vacuo*. The residue was chromatographed on silica gel with $CHCl_3$ as the eluent to give 1.5 g (79%) of ethyl 3-(3-pyrrolyl)acrylate, which was then combined with 10% NaOH (6 ml) and C_2H_5OH (3 ml). The mixture was stirred at 90 °C for 30 min. Ethanol was removed by distillation *in vacuo* and the aqueous solution was adjusted to pH 4 with 10% HCl. The resultant precipitate was collected, washed with cold water, and recrystallized from C_2H_5OH–hexane to give **3f** (0.9 g, 75%), mp 201—204 °C (dec.). EIMS *m/z*: 137 (M^+). ^{1}H-NMR (60 MHz, $(CH_3)_2SO$-d_6) δ: 5.97 (1H, d, J=16 Hz, –CH=CHCO–), 7.91 (1H, d, J=16 Hz, –CH=CHCO–). *Anal.* Calcd for $C_7H_7NO_2$: C, 61.31; H, 5.15; N, 10.21. Found: C, 61.28; H, 5.29; N, 10.10.

(*E*)-3-(2-Benzothiazolyl)acrylic Acid (3h) 2-Benzothiazolecarbaldehyde (2.5 g, 0.015 mol) was treated in a manner similar to that described above and afforded 1.6 g (52%) of recrystallized (C_2H_5OH–CH_3OH) product, mp 223—224 °C. EIMS *m/z*: 205 (M^+). ^{1}H-NMR (60 MHz, $(CH_3)_2SO$-d_6) δ: 6.82 (1H, d, J=16 Hz, –CH=CHCO–), 7.78 (1H, d, J=16 Hz, –CH=CHCO–). *Anal.* Calcd for $C_{10}H_7NO_2S$: C, 58.52; H, 3.44; N, 6.82; S, 15.62. Found: C, 58.37; H, 3.49; N, 6.72; S, 15.69.

(*E*)-3-[3-(7-Azaindolyl)]acrylic Acid (3j) A mixture of 3-(7-azaindole)carbaldehyde (1.0 g, 0.0068 mol), malonic acid (2.0 g, 0.019 mol), piperidine (0.3 ml) and pyridine (6 ml) was stirred at 40 °C for 40 h. The reaction mixture was concentrated to dryness *in vacuo*. Water (2 ml) was added to the residue. The resultant precipitate was collected and washed with CH_3OH (5 ml) to give **3j** (1.2 g, 93%), mp 218—221 °C. The product was used in the next step without further purification. EIMS *m/z*: 188 (M^+). ^{1}H-NMR (60 MHz, $(CH_3)_2SO$-d_6) δ: 6.33 (1H, d, J=16 Hz,

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–CH=CHCO–).

Acrylamides 2 and 4 (Table I). Procedure A. *N*-[4-(4-Diphenylmethyl-1-piperazinyl)butyl]-3-(2-pyrrolyl)acrylamide (2e) This compound was prepared from **3e** and 1-(4-aminobutyl)-4-diphenylmethylpiperazine (**8**)[1] with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride in a similar manner to that described previously.[2] EIMS *m/z*: 442 (M^+). IR: 1655 (C=O) cm^{-1}. ^{1}H-NMR (80 MHz, $(CH_3)_2SO$-d_6) δ: 4.25 (1H, s, –CHPh$_2$), 6.16 (1H, d, J=16 Hz, –CH=CHCO–). Compounds **2a—d**, **2f**, **2h**, **2i**, **4a**, **4c** and **4d** were prepared in a similar manner.

2a: EIMS *m/z*: 455 (M^+). IR: 1670 (C=O) cm^{-1}. ^{1}H-NMR (300 MHz, $(CH_3)_2SO$-d_6) δ: 4.25 (1H, s, –CHPh$_2$), 7.18 (1H, d, J=15.7 Hz, –CH=CHCO–), 7.56 (1H, d, J=15.7 Hz, –CH=CHCO–).

2b: EIMS *m/z*: 455 (M^+). IR: 1655 (C=O) cm^{-1}. ^{1}H-NMR (80 MHz, $(CH_3)_2SO$-d_6) δ: 4.25 (1H, s, –CHPh$_2$), 6.94 (1H, d, J=16 Hz, –CH=CHCO–).

2c: EIMS *m/z*: 455 (M^+). IR: 1650 (C=O) cm^{-1}. ^{1}H-NMR (80 MHz, $(CH_3)_2SO$-d_6) δ: 4.24 (1H, s, –CHPh$_2$), 6.79 (1H, d, J=16 Hz, –CH=CHCO–).

2d: EIMS *m/z*: 455 (M^+). ^{1}H-NMR (80 MHz, $(CH_3)_2SO$-d_6) δ: 4.31 (1H, s, –CHPh$_2$), 7.53 (1H, d, J=16 Hz, –CH=CHCO–).

2f: EIMS *m/z*: 442 (M^+). ^{1}H-NMR (80 MHz, $(CH_3)_2SO$-d_6) δ: 4.33 (1H, s, –CHPh$_2$), 6.11 (1H, d, J=16 Hz, –CH=CHCO–).

2h: EIMS *m/z*: 510 (M^+). IR: 1650 (C=O) cm^{-1}. ^{1}H-NMR (80 MHz, $(CH_3)_2SO$-d_6) δ: 4.25 (1H, s, –CHPh$_2$), 7.04 (1H, d, J=16 Hz, –CH=CHCO–).

2i: EIMS *m/z*: 492 (M^+). ^{1}H-NMR (80 MHz, $(CH_3)_2SO$-d_6) δ: 4.27 (1H, s, –CHPh$_2$), 6.57 (1H, d, J=16 Hz, –CH=CHCO–).

4a: EIMS *m/z*: 452 (M^+). IR: 1660 (C=O) cm^{-1}. ^{1}H-NMR (300 MHz, $(CH_3)_2SO$-d_6) δ: 7.19 (1H, d, J=15.7 Hz, –CH=CHCO–), 7.56 (1H, d, J=15.7 Hz, –CH=CHCO–).

4c: EIMS *m/z*: 452 (M^+). IR: 1655 (C=O) cm^{-1}. ^{1}H-NMR (80 MHz, $(CH_3)_2SO$-d_6) δ: 6.81 (1H, d, J=16 Hz, –CH=CHCO–).

4d: EIMS *m/z*: 452 (M^+). IR: 1650 (C=O) cm^{-1}. ^{1}H-NMR (80 MHz, $(CH_3)_2SO$-d_6) δ: 7.54 (1H, d, J=16 Hz, –CH=CHCO–).

Procedure B. *N*-[4-(4-Diphenylmethyl-1-piperazinyl)butyl]-3-(4-imidazolyl)acrylamide Sesquitartrate (2g) A mixture of **3g** (1.0 g, 0.0072 mol), 4-nitrophenyl trifluoroacetate (2.0 g, 0.0085 mol) and dry pyridine (35 ml) was stirred at 80 °C for 1 h. The reaction mixture was concentrated to dryness *in vacuo*, and 20 ml of DMF was added to the residue. A solution of **8** (2.3 g, 0.0071 mol) in DMF (2 ml) was added to the mixture with stirring at room temperature. After further stirring for 1 h, the mixture was concentrated to dryness *in vacuo*, and then 20 ml of 10% K_2CO_3 was added to the residue. The mixture was extracted with three 50-ml portions of $CHCl_3$. The combined extracts were dried and the solvent was removed by distillation *in vacuo*. The residue was chromatographed on silica gel with $CHCl_3$–CH_3OH (20:1) as the eluent to give an oily product, which was heated so as to dissolve in C_2H_5OH containing 0.71 g of tartaric acid. After the solution had been cooled, the precipitate was collected to give **2g** (0.8 g, 16%). EIMS *m/z*: 443 (M^+). ^{1}H-NMR (80 MHz, $(CH_3)_2SO$-d_6)δ: 4.34 (1H, s, –CHPh$_2$), 6.46 (1H, d, J=16 Hz, –CH=CHCO–).

Procedure C. *N*-[4-(4-Diphenylmethyl-1-piperazinyl)butyl]-3-[3-(7-azaindolyl)]acrylamide Fumarate (2j) This compound was prepared from **3j** and **8** by the use of DCC in a similar manner to that described previously.[1] EIMS *m/z*: 493 (M^+). ^{1}H-NMR (80 MHz, $(CH_3)_2SO$-d_6) δ: 4.29 (1H, s, –CHPh$_2$), 6.60 (1H, d, J=16 Hz, –CH=CHCO–).

Reference Compounds Ketotifen was prepared according to the literature.[18] Caffeic acid was purchased from Nacalai Tesque.

Biological Methods The tests employing rat passive cutaneous anaphylaxis and inhibition of 5-lipoxygenase were performed as described previously.[1]

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References and Notes

1) Part 1 of this series: Y. Nishikawa, T. Shindo, K. Ishii, H. Nakamura, T. Kon and H. Uno, *Chem. Pharm. Bull.*, **37**, 100 (1989).
2) Part 2 of this series: Y. Nishikawa, T. Shindo, K. Ishii, H. Nakamura, T. Kon and H. Uno, *J. Med. Chem.*, accepted for publication.
3) U. Martin and D. Römer, *Arzneim.-Forsch.*, **28**, 770 (1978).
4) log *P* is the octanol–water partition coefficient. The log *P* values of benzene, quinoline, benzothiazole, indole, 7-azaindole, thiophene, furan, pyrrole, pyridine, imidazole, pyrazine, pyrimidine and pyridazine are 2.13, 2.02, 2.01, 2.00, 1.82, 1.81, 1.34, 0.75, 0.62, −0.08, −0.22, −0.40 and −0.72, respectively. The literature cited for these values is as follows: C. Hansh and A. Leo, "Substituents Constants for Correlation Analysis in Chemistry and Biology," ed. by John Wiley and Sons, New York, Chichester, Brisbane and Toronto, 1979.
5) J. C. Castillo, E. J. De Beer and S. H. Jaros, *J. Pharmacol. Exp. Ther.*, **96**, 388 (1949).
6) R. G. Jones, E. C. Kornfeld and K. C. McLaughlin, *J. Am. Chem. Soc.*, **72**, 3539 (1950).
7) R. H. Mizzoni and P. E. Spoerri, *J. Am. Chem. Soc.*, **76**, 2201 (1954).
8) T. Sakamoto, H. Arakida, K. Edo and H. Yamanaka, *Chem. Pharm. Bull.*, **30**, 3647 (1982).
9) R. A. Jones and J. A. Lindner, *Aust. J. Chem.*, **18**, 875 (1965).
10) V. J. Demopoulos, *Org. Prep. Proced. Int.*, **18**, 278 (1986).
11) W. Ried and H. Bender, *Angew. Chem. Int. Ed. Engl.*, **2**, 380 (1963).
12) M. M. Robison and B. L. Robison, *J. Am. Chem. Soc.*, **77**, 457 (1955).
13) V. M. Rodinov and T. K. Veselovskaya, *Zh. Obshch. Khim.*, **20**, 2202 (1950) [*Chem. Abstr.*, **45**, 7106 (1951)].
14) We reported previously[1,2] that 4-(diphenylmethyl-1-piperazinyl)-butylamino and 4-(4-diphenylmethylene-1-piperidyl)butylamino groups were efficient for showing anti-PCA activity.
15) R. V. Panganamala, J. S. Miller, E. T. Gwebu, H. M. Sharma and D. G. Cornwell, *Prostaglandins*, **14**, 261 (1977).
16) W. C. Hope, A. F. Welton, C. Fiedler-Nagy, C. Batula-Bernardo and J. W. Coffey, *Biochem. Pharmacol.*, **32**, 367 (1983).
17) H. Bredereck, G. Simchen, H. Wagner and A. A. Santos, *Justus Liebigs Ann. Chem.*, **766**, 73 (1972).
18) E. Waldvogel, G. Schwarb, J. M. Bastian and J. P. Bourquin, *Helv. Chim. Acta*, **59**, 866 (1976).
19) Y. Koshihara, T. Neichi, S. Murota, A. Lao, Y. Fujimoto and T. Tatsuno, *Biochim. Biophys. Acta*, **792**, 92 (1984).

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