# Synthesis and Pharmacological Evaluation of Procaterol Derivatives Having a *tert*-Amino Group

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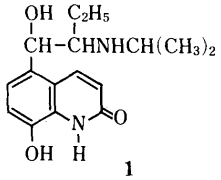
**A series of procaterol derivatives having a *tert*-amino group was synthesized. Among them, a morpholino derivative (4a, $R^1 = H$, $NR^2R^3$ = morpholino) showed $\beta$-selective and rather potent adrenoceptor stimulant activities in an *in vivo* assay using anesthetized dogs. On the other hand, a morpholinopropanol analogue (4j, $R^1 = CH_3$, $NR^2R^3$ = morpholino) showed 400 times less potent bronchodilator activity than that of 4a. Some of the compounds showed weak bronchodilator activities and weak effects on the heart. It seems that steric hindrance around the nitrogen atom of catecholamines has a significant influence on $\beta$-adrenoceptor stimulant activities. Compound 4a also showed anti-allergic action estimated in terms of the inhibition of homologous passive cutaneous anaphlaxis in rats.**

**Keywords** morpholinoethanol; *tert*-amino group; procaterol; $\beta$-adrenoceptor agonist; $\beta$-adrenoceptor stimulant activity; anesthetized dog; anti-allergic action; steric hindrance; passive cutaneous anaphlaxis

The $\beta$-adrenoceptor stimulant procaterol (**1**) has extremely potent bronchodilator activity and high $\beta$-selectivity,[1,2] and it has been widely used as a bronchodilator (Meptin) for the treatment of reversible airway obstruction. The bronchodilator activities of sympathomimetic amines having a carbostyril group are so potent that we investigated procaterol derivatives having a *tert*-amino group, although it is known that catecholamines having a *tert*-amino group show very weak $\beta$-adrenoceptor agonist activities.[3] This paper describes the synthesis of a series of procaterol derivatives having a *tert*-amino group, and pharmacological evaluations of their $\beta$-adrenoceptor stimulant activities in anesthetized dogs and anti-allergic action in a homologous PCA (passive cutaneous anaphylaxis) model in rats.




**1**

TABLE I. Amino Ketones **3** and **6**

| Compd. | $R^1$ | $NR^2R^3$ | Formula | mp (°C) | Recrystn. solvent | Yield (%) | Analysis (%) Calcd (Found) | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | C | H | N |
| **3a** | H | Morpholino | $C_{15}H_{16}N_2O_4 \cdot HCl \cdot 1.25H_2O$ | 240—242 (dec.) | Water | 15[a] | 51.88 (51.72) | 5.66 5.93 | 8.07 8.07) |
| **3b** | H | Piperidino | $C_{16}H_{18}N_2O_3 \cdot HCl \cdot 0.5H_2O$ | 239—241 (dec.) | EtOH | 53 | 57.92 (58.32) | 6.08 6.15 | 8.44 8.59) |
| **3c** | H | Dimethylamino | $C_{13}H_{14}N_2O_3 \cdot HCl \cdot 0.5H_2O$ | 284—286 (dec.) | MeOH | 25[a] | 51.92 (52.23) | 5.70 5.97 | 9.31 8.85) |
| **3d** | H | Diethylamino | $C_{15}H_{18}N_2O_3 \cdot HCl \cdot 0.5H_2O$ | 246—248 (dec.) | MeOH–$Et_2O$ | 16[a] | 56.34 (56.73) | 6.30 6.23 | 8.76 8.76) |
| **3e** | H | *N*-Cyclohexyl-*N*-methylamino | $C_{18}H_{22}N_2O_3 \cdot HBr \cdot 0.5H_2O$ | 204—206 (dec.) | Water–acetone | 82[b] | 53.47 (53.14 | 5.98 5.83 | 6.93 6.60) |
| **3f** | H | Pyrrolidino | $C_{15}H_{16}N_2O_3 \cdot HCl \cdot 0.5H_2O$ | 267—269 (dec.) | Water–acetone | 76[b] | 56.69 (57.00 | 5.71 5.92 | 8.82 8.80) |
| **3g** | H | *N*-Methylpiperazino | $C_{16}H_{19}N_3O_3 \cdot 2HCl \cdot 2.5H_2O$ | 296—298 (dec.) | Water | 12[a] | 45.83 (45.79 | 6.25 6.47 | 10.02 10.12) |
| **3h** | H | Piperazino | $C_{15}H_{17}N_3O_3 \cdot 2HCl \cdot H_2O$ | 306—308 (dec.) | Water–acetone | 39[a] | 47.63 (47.34 | 5.60 5.66 | 11.11 11.09) |
| **3i** | $CH_3$ | Diethylamino | $C_{16}H_{20}N_2O_3 \cdot HCl \cdot H_2O$ | 182—185 (dec.) | MeOH–$Et_2O$ | 55[a] | 56.06 (55.87 | 6.76 6.70 | 8.17 8.01) |
| **3j** | $CH_3$ | Morpholino | $C_{16}H_{18}N_2O_4 \cdot HBr \cdot H_2O$ | 184—186 (dec.) | Water | 24[a] | 47.89 (47.84 | 5.28 5.23 | 6.98 6.82) |
| **3k** | $CH_3$ | Imidazol-1-yl | $C_{15}H_{13}N_3O_3 \cdot HBr$ | 176—178 (dec.) | Water–acetone | 18[a] | 49.47 (49.26 | 3.89 4.18 | 11.54 11.41) |
| **3l** | $C_2H_5$ | *N*-Cyclohexyl-*N*-methylamino | $C_{20}H_{26}N_2O_3 \cdot HBr$ | 232—235 (dec.) | Water–acetone | 94[b] | 56.74 (56.51 | 6.43 6.68 | 6.62 6.55) |
| **6a** | H | Morpholino | $C_{16}H_{18}N_2O_4 \cdot HCl \cdot 0.5H_2O$ | 231—232 (dec.) | MeOH | 28 | 55.26 (55.47 | 5.80 6.08 | 8.05 8.07) |
| **6b** | H | *N*-Cyclohexyl-*N*-methylamino | $C_{19}H_{24}N_2O_3 \cdot HCl \cdot H_2O$ | 161—162 | EtOH–$Et_2O$ | 43 | 59.60 (59.82 | 7.11 7.07 | 7.32 7.41) |
| **6c** | H | Pyrrolidino | $C_{16}H_{18}N_2O_3 \cdot HCl \cdot 0.5H_2O$ | 218—219 (dec.) | EtOH | 27 | 57.92 (57.82 | 6.08 6.51 | 8.44 8.52) |
| **6d** | $C_2H_5$ | *N*-Cyclohexyl-*N*-methylamino | $C_{21}H_{28}N_2O_3$ | 133—135 | Acetone | 28 | 70.76 (70.60 | 7.92 8.04 | 7.86 7.87) |

*a*) Yield from 8-hydroxycarbostyril. *b*) Yield from the corresponding compound **6**.

TABLE II. Amino Alcohols **4** and **7**

| Compd. | $R^1$ | $NR^2R^3$ | Formula | mp (°C) | Recrystn. solvent | Yield (%) | Analysis (%) Calcd (Found) C | H | N |
|---|---|---|---|---|---|---|---|---|---|
| **4a** | H | Morpholino | $C_{15}H_{18}N_2O_4 \cdot HCl \cdot 1.25H_2O$ | 194—195 (dec.) | MeOH–$Et_2O$ | 75 | 51.58 (51.31) | 6.20 6.04 | 8.02 7.89) |
| **4b** | H | Piperidino | $C_{16}H_{20}N_2O_3 \cdot HCl \cdot 1.5H_2O$ | 146—148 (dec.) | iso-PrOH | 31 | 54.62 (54.31) | 6.88 6.90 | 7.96 7.83) |
| **4c** | H | Dimethylamino | $C_{13}H_{16}N_2O_3 \cdot HCl \cdot 2H_2O$ | 203—205 | Water–acetone | 23 | 48.68 (49.01) | 6.60 6.21 | 8.73 8.65) |
| **4d** | H | Diethylamino | $C_{15}H_{20}N_2O_3 \cdot HCl \cdot 2H_2O$ | 145—148 (dec.) | Water–acetone | 46 | 51.65 (51.89) | 7.22 7.40 | 8.03 7.73) |
| **4e** | H | *N*-Cyclohexyl-*N*-methylamino | $C_{18}H_{24}N_2O_3 \cdot HBr \cdot 1.5H_2O$ | 142—144 (dec.) | Water–acetone | *a*) | 50.95 (50.65) | 6.65 6.54 | 6.60 6.44) |
| **4f** | H | Pyrrolidino | $C_{15}H_{18}N_2O_3 \cdot HCl \cdot 1.5H_2O$ | 208—210 (dec.) | Water–acetone | 65 | 53.33 (53.47) | 6.56 7.06 | 8.29 8.44) |
| **4g** | H | Methylpiperazino | $C_{16}H_{21}N_3O_3 \cdot 2HCl \cdot 3H_2O$ | 153—155 (dec.) | Water | 78 | 44.66 (44.72) | 6.79 7.13 | 9.76 9.74) |
| **4h** | H | Piperazino | $C_{15}H_{19}N_3O_3 \cdot 2HCl \cdot 2H_2O$ | 209—210 (dec.) | Water | 53 | 45.24 (45.54) | 6.33 6.49 | 10.55 10.54) |
| **4i** | $CH_3$ | Diethylamino | $C_{16}H_{22}N_2O_3 \cdot HCl \cdot 2H_2O$ | 136—138 (dec.) | Water | 44 | 52.96 (52.66) | 7.50 7.64 | 7.72 7.45) |
| **4j** | $CH_3$ | Morpholino | $C_{16}H_{20}N_2O_4 \cdot HCl \cdot H_2O$ | 185—188 (dec.) | Water–acetone | 32 | 53.56 (53.81) | 6.46 6.32 | 7.81 7.76) |
| **4k** | $CH_3$ | Imidazol-1-yl | $C_{15}H_{15}N_3O_3 \cdot HCl \cdot 0.5H_2O$ | 243—245 (dec.) | Water | 38 | 54.47 (54.23) | 5.18 4.91 | 12.70 12.43) |
| **4l** | $C_2H_5$ | *N*-Cyclohexyl-*N*-methylamino | $C_{20}H_{28}N_2O_3 \cdot HBr \cdot 1.5H_2O$ | 128—130 (dec.) | Water | 92 | 53.10 (53.15) | 7.13 7.15 | 6.19 6.19) |
| **7a** | H | Morpholino | $C_{16}H_{20}N_2O_4 \cdot HCl$ | 249—250 (dec.) | MeOH | *a*) | 56.39 (56.25) | 6.21 6.33 | 8.22 8.24) |

*a*) Quantitative yield.

## Chemistry

A series of procaterol derivatives having a *tert*-amino group was synthesized as outlined in Chart 1. Haloketones **2** and **5** were obtained as described in our previous paper.[1] Condensation of haloketones with an appropriate *sec*-amine gave the aminoketones **3** and **6** listed in Table I, except **3e**, **3f** and **3l**, which were obtained by demethylation of the corresponding compounds **6** with HBr. Hydride reduction of the aminoketones **3** and **6** gave the amino alcohols **4** and **7a** shown in Table II. The amino alcohol **4i** was obtained as the *erythro*-isomer by repeated recrystallization from water, since the *threo*-isomer was easily soluble in water. The *threo*-isomer of **4i** was obtained from the mother liquor of the recrystallization. The nuclear magnetic resonance (NMR) spectrum ($Me_2SO$-$d_6$) of *erythro*-**4i** showed a broad singlet at 5.8 ppm and that of *threo*-**4i** showed a doublet ($J = 10.0$ Hz) at 5.2 ppm for protons on adjacent asymmetric centers, in agreement with previous findings on isomers of procaterol.[2] compounds **4j** and **4l** were obtained as *erythro*-rich mixtures (see Experimental), respectively, and compound **4k** was obtained as the *erythro*-isomer.

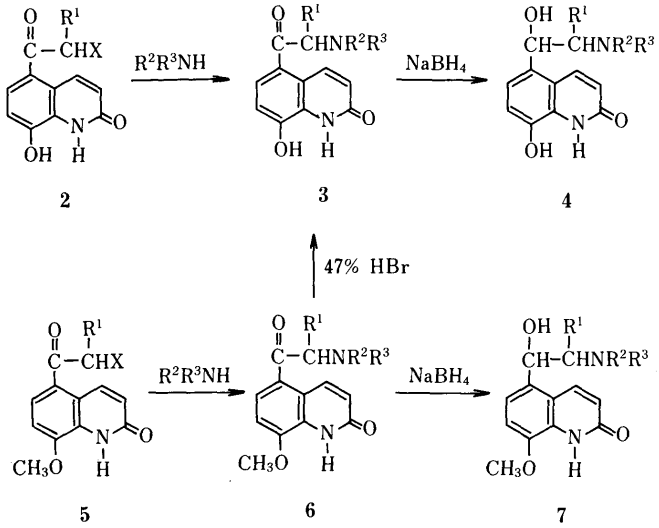



Chart 1

## Results and Discussion

The $\beta$-adrenoceptor stimulant activities of compounds **4** and **7a** were examined by *in vivo* assay in anesthetized dogs. Their bronchodilator activities and effects on the heart were evaluated in terms of inhibition of histamine-induced bronchospasm and increase in the heart rate, respectively. The results are shown in Table III.

Compound **4a**, which has a morpholino group, showed moderately potent $\beta$-adrenoceptor stimulant activities. Its bronchodilator activity was 45 times less potent than that of *l*-isoproterenol and 22 times less active than that of procaterol. The effect of **4a** on the heart was 500 times less potent than that of *l*-isoproterenol, and the separation ratio value of compound **4a** was 11.1. On the other hand, compound **7a** lacked pharmacological activities since the 8-hydroxyl group of **4a** is converted to a methoxyl group. These results indicate that the morpholinoethanol **4a** is a $\beta$-selective adrenoceptor agonist. The morpholinopropanol derivative **4j** showed 400 times less bronchodilator activity than that of **4a**. The significant decrease in pharmacological activities of **4j** might be derived from the increase in steric hindrance around the

Table III. β-Adrenoceptor Stimulant Activities in Dogs

| Compd. | Inhibition of broncho-constriction, equipotent dose at $ED_{50}$ [a] | Increase in heart rate, equipotent dose at $ED_{25}$ [a] | Separation ratio [b] |
|---|---|---|---|
| **4a** | 45 | 500 | 11.1 |
| **4b** | c) | d) | |
| **4c** | e) | f) | |
| **4d** | 730 | g) | |
| **4e** | h) | h) | |
| **4f** | h) | h) | |
| **4g** | h) | h) | |
| **4h** | 2900 | i) | |
| **4i** | 1700 | 27000 | 15.9 |
| **4j** | 18000 | e) | |
| **4k** | 4100 | 52000 | 12.7 |
| **4l** | e) | e) | |
| **7a** | e) | j) | |
| Procaterol | 2.03 | 50.5 | 24.9 |
| *l*-Isoproterenol | 1.00 | 1.00 | 1 |

*a*) Relative to *l*-isoproterenol = 1.00. *b*) Increase in heart rate, $ED_{25}$, divided by inhibition of bronchoconstriction, $ED_{50}$. *c*) No significant action in guinea pig tracheal test. The assay is described in ref. 1. *d*) No significant effect in guinea pig atrial test. The assay is described in ref. 1. *e*) No significant action at a dose of 1 mg/kg. *f*) $ED_{14}$ at 1 mg/kg. *g*) $ED_{20}$ at 300 μg/kg. *h*) Not tested. *i*) No significant effect at 300 μg/kg. *j*) $ED_{18}$ at 1 mg/kg.

nitrogen atom of the morpholino group. The diethylaminoethanol **4d** and the diethylaminopropanol **4i** showed 730 times less potent and 1700 times less potent bronchodilator activity, respectively, than that of *l*-isoproterenol, and the effects on the heart of these compounds were also very weak. The piperazinoethanol **4h** and the imidazol-1-ylpropanol **4k** also showed weak pharmacological activities, and compounds **4b**, **4c** and **4l** showed no significant activities.

From studies on site-directed mutagenesis of β-adrenergic receptors, Dixon *et al.*[4] and Strader *et al.*[5] reported that aspartic acids of the receptor are essential for the expression of receptor function. Aspartic acid[113] of the receptor may associate with the amino group of noradrenaline and other catecholamine derivatives, and their interaction may provide a basis for receptor-agonist correlations.[6] The effect of steric hindrance observed between activities of **4a** and **4j** may be one of the reasons for the weak β-adrenoceptor stimulant activities of catecholamines having a *tert*-amino group.

The anti-allergic action of compound **4a** was investigated in the homologous PCA model in rats, because β-adrenoceptor agonists such as procaterol showed potent anti-allergic actions.[7] The results are shown in Table IV. Compound **4a** showed dose-dependent inhibitory activity against homologous PCA in rats on i.v. injection at 10 to 1000 μg/kg, and the activity was approximately 10 times more potent than that of disodium cromoglycate (DSCG). These results indicate that compound **4a** may be useful as a bronchodilator.

Table IV. PCA in Rats

| Compd. | | Amount of dye (μg/site) | Inhibition (%) |
|---|---|---|---|
| Control | | 18.0 | |
| **4a** | 10 μg/kg | 13.4 | 25.5 |
| | 100 μg/kg | 5.9 | 67.0 |
| | 1000 μg/kg | 2.1 | 88.5 |
| DSCG | 100 μg/kg | 17.8 | 1.1 |
| | 1000 μg/kg | 7.7 | 57.3 |

## Experimental

**Chemistry** Melting points were determined by the capillary method and are given as uncorrected values. Elemental analyses were done in a Yanagimoto MT-2 CHN recorder. NMR spectra were recorded with a Hitachi R-20B spectrometer, and the data supported the indicated structure of each compound.

**Typical Procedures. A. 8-Hydroxy-5-morpholinoacetylcarbostyril (3a)** Crude 5-chloroacetyl-8-hydroxycarbostyril (40 g, obtained from 20 g (0.125 mol) of 8-hydroxycarbostyril)[1] and 100 ml of morpholine were mixed under cooling, and stirred at room temperature for 1 h. The reaction mixture was washed three times with $Et_2O$ to remove excess amine, suspended in 300 ml of water, and washed three times with $Et_2O$. The water layer was acidified with concentrated HCl to pH 1 and evaporated. EtOH (300 ml) was added to the residue, and the solid was collected and dissolved in water. The water layer was made alkaline to pH 9 with aqueous KOH solution and extracted with *n*-BuOH (2 l). The *n*-BuOH layer was acidified to pH 1 with concentrated HCl and evaporated. The residue was recrystallized from water to give 6.5 g (15% yield from 8-hydroxycarbostyril) of 8-hydroxy-5-morpholinoacetylcarbostyril **3a** as the hydrochloride 1.25-hydrate, mp 240—242 °C (dec.).

The aminoketones **3b—d** and **3g—k** were obtained in a similar manner. The acid salts of the aminoketones **3** were generally hygroscopic and many of them were hydrated.

**B. 8-Methoxy-5-morpholinoacetylcarbostyril (6a)** A mixture of 15 g (59 mmol) of 5-chloroacetyl-8-methoxycarbostyril[1] and 100 ml of morpholine was stirred at 55 °C for 3 h. After cooling, a portion of $Et_2O$ was added to the reaction mixture. The precipitate was collected, washed with $Et_2O$, and extracted with 1 l of $CHCl_3$. The $CHCl_3$ layer was washed with water, dried over $Na_2SO_4$, and evaporated. The resulting solid was dissolved in MeOH, acidified to pH 1 with concentrated HCl and evaporated. The residue was recrystallized from MeOH to give 5.7 g (28%) of 8-methoxy-5-morpholinoacetylcarbostyril **6a** as the hydrochloride hemihydrate, mp 231—232 °C (dec.).

The aminoketones **6b—d** were obtained in a similar manner.

**C. 5-[2-(*N*-Cyclohexyl-*N*-methylamino)butyryl]-8-hydroxycarbostyril (3l)** A solution of 3.26 g (9.2 mmol) of 5-[2-(*N*-cyclohexyl-*N*-methylamino)butyryl]-8-methoxycarbostril (**6d**) in 40 ml of 47% HBr was refluxed at 140 °C for 20 h. The reaction mixture was evaporated after cooling and extracted with water. The water layer was evaporated and the residue was recrystallized from water–acetone to give 3.7 g (94%) of 5-[2-(*N*-cyclohexyl-*N*-methylamino)butyryl]-8-hydroxycarbostyril **3l** as the hydrobromide, mp 232—235 °C (dec.).

**D. 5-(1-Hydroxy-2-morpholinoethyl)-8-hydroxycarbostyril (4a)** A suspension of 6.5 g (18.8 mmol) of the morpholinoketone **3a** in 300 ml of MeOH was made alkaline with KOH–MeOH solution to pH 8 under stirring and cooling in ice-water, and 15 g of $NaBH_4$ was added in small portions. After reduction was over, the mixture was acidified to pH 1 with concentrated HCl, the precipitate was removed, and the solvent was evaporated off. The residue was extracted with MeOH, the solvent was evaporated off, and the crystalline solid was recrystallized from water to give 4.9 g (75%) of 5-(1-hydroxy-2-morpholinoethyl)-8-hydroxycarbostyril **4a** as the hydrochloride 1.25-hydrate, mp 194—195 °C (dec.).

The amino alcohols **4b—h** and **7a** were obtained in a similar manner. The acid salts of amino alcohols were usually hygroscopic and many of them were hydrated.

**E. *erythro*-5-(2-Diethylamino-1-hydroxypropyl)-8-hydroxycarbostyril (4i)** A solution of 10.0 g (29 mmol) of 5-(2-diethylaminopropionyl)-8-hydroxycarbostyril hydrochloride monohydrate **3i** in 100 ml of water was made alkaline to pH 8 with aqueous NaOH solution, and 2.0 g of $NaBH_4$ was added in small portions under stirring and cooling. After 3 h, the reaction mixture was acidified to pH 1 with concentrated HCl, and 300 ml of MeOH was added and evaporated to remove methyl borate. The residue was recrystallized three times from water to give 4.5 g (44%) of *erythro*-5-(2-diethylamino-1-hydroxypropyl)-8-hydroxycarbostyril **4i** as the hydrochloride dihydrate, mp 136—138 °C (dec.). NMR ($Me_2SO$-$d_6$): δ 5.8 (s(br), 1H, C<u>H</u>-OH). A small amount of acetone was added to the mother liquor of the first recrystallization, and the precipitate was collected and recrystallized from water to give 0.2 g (2%) of *threo*-**4i**, mp 206—208 °C (dec.). NMR ($Me_2SO$-$d_6$): δ 5.2 (d, 1H, $J$ = 10.0 Hz, C<u>H</u>-OH).

The *erythro*: *threo* ratios of other compounds were determined from the NMR spectra as follows: compound **4j** 59:41, compound **4k** 100:0 and compound **4l** 67:33.

**Pharmacology. Methods. A. β-Adrenoceptor Agonist Assay Using Anesthetized Dogs** Adult male mongrel dogs, weighing 10—15 kg, were anesthetized by intravenous injection of 30 mg/kg body weight of sodium

pentobarbital. The anesthetized dogs were placed on their backs and a cannula was inserted into the trachea. Histamine at a dose of 10 μg/kg body weight was given as a bronchoconstrictor 1 min after injecting aqueous solutions of various concentrations of the test compounds through the femoral vein. Artificial respiration was carried out by the Konzett–Rössler method.[8] The volume of air inhaled was measured with a differential transducer (San-ei Sokki, Type 1236) to determine the bronchial resistance and the values obtained were recorded on a polygraph. The $ED_{50}$ values of the test compounds were determined from dose–response curves and compared with that of *l*-isoproterenol. The heart rate was measured simultaneously with a heart rate meter triggered from the blood pressure through a pressure transducer (San-ei Sokki, Type 1236) attached to the cannulated femoral artery. The $ED_{25}$ values of the test compound (producing an increase in the heart rate of 25 beats/min) were determined from dose–response curves and compared with that of *l*-isoproterenol. To inhibit spontaneous respiration and to maintain anesthetic conditions constant during the test period, sodium pentobarbital was infused continuously during the experiment at a dose of 4 mg/kg body weight per hour, using an automatic injector.

**B. PCA in Rats** Antiserum containing homocytotropic antibody was obtained from rats that had been immunized with 2,4-dinitrophenyl-coupled ascaris (DNP-As) mixed with killed *Bordetella pertussis* according to Tada and Okumura.[9] The antibody titer of this serum (rat anti-DNP-As serum) was about 1 : 128 as estimated from the 48 h PCA. The antiserum diluted 20-fold with 0.9% saline was injected intradermally in 0.1 ml dose into 3 sites on the shaved backs of normal male Wister rats weighing 160 to 190 g. The same dose of physiological saline was similarly injected into the other side. After 48 h, the animals were given 1.0 ml of 0.5% Evans blue solution containing 2.0 mg of antigen intravenously. Thirty min later, the animals were killed by exsanguination and the skins were removed to measure the PCA bluing lesion. The amount of the dye was then estimated colorimetrically after extraction by the method of Harada *et al.*[10] The test compounds were dissolved in physiological saline, and were given intravenously to rats immediately before challenge with the antigen. Their responses ($n=4$) were expressed as percent inhibition of the leakage of Evans blue caused by PCA.

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