Studies on a New Antiallergic Pyridinecarboxamide TA-5707F and Its Sodium Salt (TA-5707)

I. Inhibition of IGE-Induced Passive Cutaneous Anaphylaxis (PCA) in Rats

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Abstract—Effects of TA-5707F [6-methyl-N-(1H-tetrazol-5-yl)-2-pyridinecarboxamide] and its sodium salt (TA-5707) on IgE-induced homologous PCA in rats were investigated. 1. Both TA-5707 and TA-5707F were found to be orally effective inhibitors of rat PCA. Maximum activity by oral administration was obtained when they were administered 5 min before the challenge. Their ID50’s under these conditions were both approximately 1 mg/kg. Administration 5 min after the challenge was no longer effective. 2. TA-5707 was also effective by intravenous administration, and its ID50, ca. 0.1 mg/kg, was less than that of disodium cromoglycate (DSCG). 3. The PCA-inhibitory activity of TA-5707 was not affected by adrenalectomy and adrenomedullectomy. 4. Daily administration of TA-5707 or TA-5707F for 8 days did not induce drug tolerance. 5. Tachyphylaxis and cross-tachyphylaxis were observed when the PCA-inhibitory activities of TA-5707 and DSCG were tested after intravenous pretreatment with a large dose (ca. 30 times the ID50) of either drug, but not after oral pretreatment with a therapeutic dose of TA-5707 or TA-5707F.

Inhibitors of immediate (type I) allergic reactions can be clinically useful for treatment of allergic bronchial asthma, urticaria, eczema, rhinitis, hay fever and the like. DSCG is a representative antiallergic and is being widely used for treatment of allergic asthma and rhinitis. However, DSCG is available only for parenteral use, because it is not absorbed from the intestinal tract. Thus, great efforts have been made to develop orally active antiallergics.

We have investigated the effect of substitution of other heterocycles for the chromone structure of DSCG on the antiallergic activity using PCA in rats as the test system and arrived at a new series of orally effective antiallergics—N-tetrazolyl pyridinecarboxamides (1–3). Out of these, we have selected 6-methyl-N-(1H-tetrazol-5-yl)-2-pyridinecarboxamide (TA-5707F, Fig. 1) and its sodium salt (TA-5707, Fig. 1) for further studies. This report describes a

Fig. 1. Chemical structures of TA-5707F (I, R=H), TA-5707 (I, R=Na) and their structural analogue, “compound II” (II).
detailed study on the inhibition of rat PCA by TA-5707F and TA-5707.

Materials and Methods

Rats: Male Sprague-Dawley rats (ca. 200 g in body weight) were purchased from Shizuoka Laboratory Animal Center and maintained on the laboratory chow before use.

Rat anti-Ascaris antiserum: Rats were immunized twice (day 0 and 7) with *Ascaris suum* proteins (s.c.) along with *Bordetella pertussis* (i.p.) as adjuvant (day 0 only), and they were bled from the abdominal aorta under ether anesthesia on day 21 (4). IgE activity of the antisera obtained was confirmed by its heat lability and long-lasting (7 days at least) fixation on the rat skin in homologous PCA. PCA titers of the antisera were generally over 60.

Rat PCA: Rat PCA was induced as described elsewhere (1) except that the rats were challenged with antigen 48 hr after the sensitization. In most experiments, 15-fold diluted antisera were used for passive sensitization. The magnitude of PCA response was expressed as the product of the largest diameter (cm) and the perpendicular diameter (cm) of the blueing area.

Evaluation of PCA-inhibitory activity of test compounds: Test compounds were dissolved in saline or suspended in 0.5% carboxymethylcellulose (CMC) solution and administered either orally or intravenously. Control rats were either untreated or treated with vehicle. PCA-inhibitory activity was expressed as percent inhibition.

Adrenalectomy and adrenomedullectomy: A slit of 1–2 cm in length was made on the abdominal skin of rats anesthetized with ether, the adrenal gland or medulla was excised with a heat-sterilized ring pincette and De-wecker iris scissors, and the slit was sutured. The peritoneal cavity and the abdominal skin were moistened with a 0.1% solution of a semi-synthetic penicillin, aspoxicillin (Tanabe Seiyaku Co., Ltd.). The operated rats were kept for 1–2 days with free access to saline instead of water until use.

Chemicals: TA-5707F and TA-5707 were synthesized at the Pharmaceutical Technics Division of Tanabe Seiyaku Co., Ltd. and “compound II” (Fig. 1) at the Organic Chemistry Research Laboratory of the same company. DSCG was used in the form of a commercial product, Intal® (Fujiwasa Pharmaceutical Co., Ltd.), a 1:1 mixture of DSCG and lactose. Lactose did not affect PCA at the dose of 3 mg/kg given intravenously at the time of challenge.

Determination of pKa for TA-5707F: One tenth N HCl containing NaCl to adjust ion strength and six Britton-Robinson’s buffer solutions (5) with various pH’s (1.4, 2.4, 3.1, 4.2, 5.0, 6.0 and 7.0 after dilution) were prepared and diluted 2.5 times with water. The final ion strengths of these solutions were all 0.176. TA-5707 was dissolved in these solutions (12.4 µg/ml) and its UV absorption spectra (210–360 nm) were measured in reference to the corresponding buffer solutions. Since the greatest change in absorption was seen around 240 nm as the pH was varied, optical densities at 240 nm were plotted against pH to draw a pH-absorbance curve, from which the pKa values were deduced.

Results

Time course of the inhibitory effect of orally administered TA-5707 and TA-5707F on rat PCA: Time courses of the inhibitory effect of TA-5707 and TA-5707F on rat PCA at three doses are shown in Fig. 2. The inhibition was clearly dose-dependent. It was maximal at 5 min after oral administration. The inhibitory effect decreased relatively rapidly after the peak. There was practically no activity at 60 min. Although a significant inhibition was observed when the rats were treated immediately after challenge, there was no effect when medication was delayed until 5 min after the challenge (Table 1).

Dose-response relationship of the PCA-inhibitory activities of TA-5707 and TA-5707F: Dose-inhibition relationships of TA-5707, TA-5707F and DSCG are shown in Fig. 3. When administered 5 min before the challenge, the ID50 values for TA-5707 and TA-5707F were 0.9 mg/kg (95% confidence limit: 0.6–1.6 mg/kg) and 0.6 (0.4–0.9) mg/kg, respectively (Fig. 3A). There was no inhibition by orally administered DSCG.
Fig. 2. Time courses of the inhibitory effect of orally administered TA-5707 and TA-5707F on rat PCA.
One, 3 or 10 mg/kg of TA-5707 (A; N=3–10) or TA-5707F (B; N=6–8) was orally administered to sensitized rats at the time indicated on the abscissa prior to challenge.

Table 1. Effect of TA-5707 on rat PCA

| Administration (p.o.) | Dose (mg/kg) | 1 | 3 |
|-----------------------|--------------|---|---|
| Control               |              | 1.54±0.04 (4) |  |
| 5 min before challenge|              | 0.74±0.04*** (3) | 0±0*** (4) |
| immediately after challenge|            | 1.11±0.16 (5) | 0.83±0.09*** (4) |
| 5 min after challenge |              | 1.63±0.03 (4) | 1.65±0.09 (4) |

Dimensions of the PCA reaction (cm²) are shown with standard errors of the mean. Numbers of rats are shown in parentheses. ***P<0.001 in Student's t-test.

On administration by the intravenous route at the time of challenge, TA-5707 (ID50=0.11 mg/kg, 95% confidence limit: 0.08–0.15 mg/kg) showed an activity ca. 8 times as high as that of DSCG (ID50=0.86 mg/kg) (Fig. 3B).

Influence of adrenomedullectomy and adrenalectomy on the PCA-inhibitory activity of TA-5707: Involvement of adrenal functions in the PCA reaction and its inhibition by TA-5707 was examined. PCA reaction in adrenomedullectomized rats was somewhat enhanced when compared to intact or sham-operated rats (Table 2). There was no difference in the inhibitory activity of TA-5707 between the sham-operated and adrenomedullectomized groups, although the inhibitory effects in both operated groups were smaller than in the intact control (Table 2, Exp. 1). A dose-dependent inhibition was apparent in the adrenomedullectomized rats. Dose-dependent inhibition was also observed in the adrenalectomized rats. The activity was not significantly different from that in
Fig. 3. Inhibition of rat PCA by TA-5707, TA-5707F and DSCG. (A) TA-5707 (●) or TA-5707F (▲) was orally administered 5 min before challenge, N=5–8. (B) TA-5707 (●) or DSCG (○) was intravenously administered at the time of challenge, N=5–16. Standard errors of the mean are shown by vertical lines.

sham-operated rats at each dose level (Table 2, Exp. 2).

Effect of daily administration of TA-5707 and TA-5707F on their PCA-inhibitory activities: PCA-inhibitory activity of TA-5707 was evaluated after daily administration of the drug at the dose of 1.5 mg/kg/day for 8 days. As shown in Table 3 (Exp. 1), there was no significant difference in the percent inhibition attained by 2 mg/kg of TA-5707 between the drug- and saline-pretreated groups. On the contrary, the activity of an analogue of TA-5707, "compound II" (Fig. 1), was lost after daily administration prior to the PCA test. In a similar experiment, repeated administration of TA-5707F did not induce tolerance, either (Table 3, Exp. 2).

Effect of pretreatment with TA-5707 and DSCG on their PCA-inhibitory activities: DSCG is known to induce tachyphylaxis both in vivo and in vitro (6–11). In order to examine if TA-5707 induces tachyphylaxis to itself (autotachyphylaxis) or if there is cross-tachyphylaxis between TA-5707 and DSCG, an intravenous dose approximately 30 times the intravenous ID50 of TA-5707 or DSCG was administered to rats one hr before the PCA-inhibition test of each drug. Significant reductions of the PCA-inhibitory activities of TA-5707 and DSCG were seen in all the pretreatment groups (Table 4), i.e., not only autotachyphylaxis for either drug but also cross-tachyphylaxis between the two were induced under these conditions.

However, oral pretreatment of rats with 1 (the approximate ID50) or 3 mg/kg of TA-5707 and TA-5707F did not induce tachyphylaxis in the PCA-inhibition by either drug (Table 5). In these studies, none of the primary treatments affected the subsequent PCA response in control rats.

pKa’s for TA-5707F: From the pH-absorption (at 240 nm) curve (not shown), pKα₂ and pKα₁ were estimated to be ca. 4.2 and less than 2, respectively.

Discussion

TA-5707F was originally derived from DSCG, although it has a much simpler chemical structure (1–3). The common structural requirement for their antiallergic activities seems to be the presence of an acidic side chain at the 2-position of a
Table 2. Effect of TA-5707 on PCA in adrenomedullectomized and adrenalectomized rats

| Experiment | Group | Rats                  | Dose of TA-5707 (mg/kg) | N | PCA response (cm²) | Inhibition of PCA (%) |
|------------|-------|-----------------------|------------------------|---|-------------------|-----------------------|
| 1          | 1     | Intact                | 0                      | 6 | 1.54±0.16a        |                       |
| 2          |       | Intact                | 3                      | 5 | 0.45±0.12 (P<0.001)b | 70.8± 7.8 P<0.05 from group 4 |
| 3          |       | Sham-operated         | 0                      | 6 | 1.53±0.19         |                       |
| 4          |       | Sham-operated         | 3                      | 5 | 0.77±0.06 (P<0.01) | 49.7± 3.9             |
| 5          |       | Adrenomedullectomized | 0                      | 6 | 2.05±0.14         |                       |
| 6          |       | Adrenomedullectomized | 3                      | 7 | 0.98±0.23 (P<0.01) | 52.2±11.2 NSc from group 4 |
| 7          |       | Adrenomedullectomized | 10                     | 4 | 0.30±0.17 (P<0.001) | 85.4± 8.3             |

2        | 1     | Sham-operated         | 0                      | 5 | 1.10±0.14         |                       |
| 2          |       | Sham-operated         | 1                      | 5 | 0.89±0.06 (NS)    | 19.1± 5.5             |
| 3          |       | Sham-operated         | 3                      | 5 | 0.41±0.19 (P<0.05) | 62.7±17.3             |
| 4          |       | Adrenalectomized      | 0                      | 5 | 1.29±0.09         |                       |
| 5          |       | Adrenalectomized      | 1                      | 5 | 1.01±0.15 (NS)    | 21.7±11.6 NS from group 2 |
| 6          |       | Adrenalectomized      | 3                      | 5 | 0.61±0.07 (P<0.001) | 52.7± 5.4 NS from group 3 |
| 7          |       | Adrenalectomized      | 10                     | 4 | 0.06±0.06 (P<0.001) | 95.3± 4.7             |

a standard errors of the mean.  b Student's t-test.  c difference was not significant.
Table 3. Effect of repeated administration of TA-5707 and its analogue "compound II" on their PCA inhibitory activities

| Experiment | Group | Pretreatment (day 1–8) | Test compound (day 9) | N  | PCA response (cm²) | Inhibition (%) |
|------------|-------|------------------------|-----------------------|----|-------------------|---------------|
| 1          | 1     | Saline                 | Saline                | 5  | 1.25±0.13         |               |
| 2          | 1     | Saline                 | TA-5707 2 mg/kg       | 5  | 0.40±0.13         | 68.0 (to group 1) |
| 3          | 1     | TA-5707 1.5 mg/kg/day  | Saline                | 6  | 0.99±0.08         | NS           |
| 4          | 1     | TA-5707 1.5 mg/kg/day  | TA-5707 2 mg/kg       | 7  | 0.29±0.15         | 70.7 (to group 3) |
| 5          | 1     | Saline                 | "Compound II" 5 mg/kg | 5  | 0.49±0.16         | 60.8 (to group 1) |
| 6          | 1     | "Compound II" 4 mg/kg/day | Saline                | 6  | 1.03±0.07         | P<0.02       |
| 7          | 1     | "Compound II" 4 mg/kg/day | "Compound II" 5 mg/kg | 6  | 1.08±0.11         | 0 (to group 6) |

| Experiment | Group | Pretreatment (day 1–8) | Test compound (day 9) | N  | PCA response (cm²) | Inhibition (%) |
|------------|-------|------------------------|-----------------------|----|-------------------|---------------|
| 2          | 1     | 0.5% CMC               | 0.5% CMC              | 6  | 1.25±0.18         |               |
| 2          | 2     | 0.5% CMC               | TA-5707F 0.7 mg/kg    | 7  | 0.91±0.10         | 27.2 (to group 1) |
| 3          | 2     | 0.5% CMC               | TA-5707F 2 mg/kg      | 7  | 0.23±0.13         | 81.6 (to group 1) |
| 4          | 2     | TA-5707F 1.5 mg/kg/day | 0.5% CMC              | 7  | 1.10±0.10         | NS           |
| 5          | 2     | TA-5707F 1.5 mg/kg/day | TA-5707F 0.7 mg/kg    | 7  | 0.53±0.18         | 51.8 (to group 4) |
| 6          | 2     | TA-5707F 1.5 mg/kg/day | TA-5707F 0.7 mg/kg    | 7  | 0 ± 0             | 100 (to group 4) |

Rats were orally pretreated with saline, TA-5707 or "compound II" (Exp. 1), or with 0.5% CMC solution or TA-5707F (Exp. II) for 8 days, and the PCA-inhibition test was performed on the 9th day 24 hr after the last pretreatment gavage. * standard errors of the mean. † no significant difference from group 1 in each Experiment. * difference was not significant.
substituted heterocyclic ring. What is unique about TA-5707F is an efficient absorption from the gastrointestinal tract as shown by the time course of PCA inhibition with a peak at 5 min after oral administration (Fig. 2B).

Table 4. Effects of intravenous pretreatment with TA-5707 and DSCG on their PCA-inhibitory activities

| Experiment | Primary treatment (i.v.) | Secondary treatment (i.v.) | Saline | TA-5707 | DSCG |
|------------|--------------------------|--------------------------|--------|---------|-------|
|            |                          | PCA response (cm²)       |        |         |       |
| 1          | Saline                   | 1.18±0.05 (22)           | 60.4±8.4 (12) | 94.5±3.1 (20) | 61.4±9.2 (16) | 100±0 (12) |
|            | TA-5707 (3 mg/kg)        | 1.22±0.09 (10)           | 27.2±4.0 (9) | 62.3±7.8 (9) | 26.8±4.1 (13) | 65.3±10.2 (7) |
| 2          | Saline                   | 0.95±0.04 (8)            | 47.8±7.8 (5) | 100±0 (5) | 74.5±6.8 (8) | 100±0 (8) |
|            | DSCG (30 mg/kg)          | 1.13±0.10 (14)           | 19.1±4.1 (13) | 80.3±6.3 (12) | 44.4±7.3 (15) | 78.6±7.3 (13) |

Rats were pretreated i.v. either with saline, TA-5707 or DSCG. One hr later, the PCA-inhibitory activities of TA-5707 or DSCG administered i.v. were evaluated and expressed as percent inhibition to the saline-treated control within each of the differently pretreated groups. Numbers of rats are shown in parentheses. *P<0.05, **P<0.01, ***P<0.001 in Student’s t-test.

Table 5. Effects of oral pretreatment with TA-5707 and TA-5707F on their PCA-inhibitory activities

| Experiment | Compound | Dose of primary treatment (mg/kg, p.o.) | Dose of secondary treatment (mg/kg, p.o.) | Control | 1 | 3 |
|------------|----------|---------------------------------------|----------------------------------------|---------|---|---|
|            |          | PCA response (cm²)                     | Inhibition of PCA response (%)         |         |   |   |
| 1          | TA-5707  | Saline                                | 1.25±0.10 (4)                          | 49.6±8.5 (5) | 77.4±11.7 (4) |
|            |          |                                       | 1.31±0.07 (5)                          | 49.1±11.3 (5) | 88.5±6.6 (4) |
|            |          |                                       | 1.09±0.16 (4)                          | 57.4±12.4 (5) | 81.0±19.0 (4) |
| 2          | TA-5707F | 0.5% CMC                              | 1.26±0.09 (4)                          | 69.2±13.7 (5) | 94.6±5.4 (4) |
|            |          |                                       | 1.17±0.10 (4)                          | 50.8±13.6 (5) | 100±0 (3) |
|            |          |                                       | 1.16±0.16 (4)                          | 80.9±9.6 (5) | 100±0 (4) |

Rats were pretreated orally with TA-5707, TA-5707F or vehicle 1 hr before the PCA-inhibition test in which the secondary dosage was given 5 min before challenge. The PCA-inhibitory activities of TA-5707 and TA-5707F are expressed as percent inhibition to the control rats which were treated 5 min before challenge with saline (Exp. 1) or with 0.5% CMC solution (Exp. 2).

TA-5707F was shown to have two pKa’s: 4.2 (pKa₂) and less than 2 (pKa₁). This would mean that, when orally administered, the sodium salt TA-5707 will be transformed in the stomach to TA-5707F or further to the protonated form, for the pH of rat gastric juice is ca. 0.9. Hence, oral treatment of rats with TA-5707 or TA-5707F would make no difference in their pharmacological activity. Indeed, there was no essential difference between the two compounds in their time courses (Fig. 2) and dose-response relationships (Fig. 3A) of PCA-inhibition. Thus, TA-
5707 and TA-5707F may be considered bioequivalent. Therefore, some of the data in which only TA-5707 was used would be reproduced with TA-5707F.

The time course with an early peak followed by a rapid decline suggests not only a rapid absorption from the gastrointestinal tract but also a prompt excretion out of the body. These were confirmed by pharmacokinetic studies in rats, which showed a plasma concentration-time profile similar to the time course of PCA-inhibition and a relatively rapid urinary excretion of the drug and its metabolites (M. Yoshikawa et al., unpublished data). This relatively short-lived effect of TA-5707F (and TA-5707) may be unique to the rat, because its antiallergic effect is much more long-lasting in parallel with a slower decay of its circulating concentrations both in dogs (K. Tsuzurahara et al., unpublished data) and man (12), probably reflecting species differences in drug metabolism.

TA-5707 was no longer effective if its administration is delayed until 5 min after challenge, when anaphylactic release of the chemical mediators from the mast cells would have been completed in the present PCA system. This failure of "belated" TA-5707 administration to inhibit PCA reaction, therefore, suggests that the drug may inhibit the release, rather than the actions, of the anaphylactic mediators.

The presence of cross-tachyphylaxis between TA-5707 and DSCG is another indirect piece of evidence that TA-5707 works as an inhibitor of anaphylactic release of mediators, for DSCG is known to inhibit anaphylactic release (13, 14). ICI 74,917 (6), PRD-92-Ea (7), and traxanox (8), which have been reported to inhibit anaphylactic release, also induce cross-tachyphylaxis to DSCG. It should be stressed here that the tachyphylaxis was brought about only when large doses (ca. 30 times the ID50) of the compounds were intravenously administered one hr before the PCA test, and that oral pretreatments with therapeutic doses (1 or 3 mg/kg) did not cause tachyphylaxis (Table 5). These results could be explained by the hypothesis proposed by Marshall et al. (9) that tachyphylaxis is related to the continued occupation of a receptor by the drug molecule, which physically prevents further access of new drug molecules to the receptor. Administration of a large amount of TA-5707 might lead to such a continued occupancy of the receptors.

Inhibition of anaphylactic release as the mechanism of antiallergic action is further supported by our observations that TA-5707 inhibited histamine release from the sensitized rat peritoneal mast cells (15) and that it showed no antagonistic activity against dye leakage on the rat skin induced by intracutaneous injection of histamine, serotonin, bradykinin or leukotriene D4 (15, 16).

TA-5707 was fully active in the PCA-inhibitory action, either in adrenomedullectomized or in adrenalectomized rats, compared to those in sham-operated rats (Table 2). Therefore, the effect of TA-5707 could not be mediated by the action of catecholamines or corticosteroids, which are known to inhibit PCA reactions (4, 17–19). However, TA-5707 was less active in sham-operated than intact rats (Table 2, Exp. 1). The stress of operation might have induced a reduction of sensitivity to the drug in these rats. Furthermore, it was found that the magnitudes of the PCA reaction in adrenomedullectomized rats were greater than in intact or sham-operated rats. This might suggest that endogenous catecholamines constantly suppress the allergic responses in normal rats, but the augmentation of the PCA reaction was not seen when the whole adrenal gland was excised (Table 2, Exp. 2).

As antiallergic drugs are repeatedly administered in the clinical field, it is important to test whether the candidate compounds induce drug-tolerance. Neither TA-5707 nor TA-5707F induced tolerance in inhibition of the PCA reaction (Table 3). This fact is considered to be a great advantage of TA-5707 and TA-5707F over their structural analogue "compound II" (Fig. 1), which also has antiallergic activity (20).

The oral ID50 values of TA-5707 and TA-5707F for inhibition of PCA in rats were 0.9 and 0.6 mg/kg, respectively, being lower than those of other orally active antiallergics hitherto reported (21–23). TA-5707 and TA-5707F also suppressed antigen-induced
bronchoconstriction in rats at similarly low doses when given by the intraduodenal and intravenous routes (16). Orally administered TA-5707 was effective in early clinical trials in patients with allergic rhinitis (24), and it suppressed the allergic skin reaction in volunteers sensitive to house dust (12). The oral LD50 of TA-5707 in rats was ca. 1 g/kg (16), and serious untoward effects have not so far been observed. Thus, TA-5707 and TA5707F may prove to be clinically useful as orally effective antiallergic agents.

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References
1 Honma, Y., Sekine, Y., Hashiyama, T., Takeda, M., Ono, Y. and Tsuzurahara, K.: Studies on antiallergic agents. 1. Phenyl-substituted heterocycles with a 5-tetrazolyl or N-(5-tetrazolyl)carbamoyl group. Chem. Pharm. Bull. (Tokyo) 30, 4314-4324 (1982)
2 Honma, Y., Oda, K., Hashiyama, T., Hanamoto, K., Nakai, H., Inoue, H., Ishida, A., Takeda, M., Ono, Y. and Tsuzurahara, K.: Antiallergic agents. 2. N-(1H-tetrazol-5-yl)-6-phenyl-2-pyridinecarboxamides. J. Med. Chem. 26, 1499-1504 (1983)
3 Honma, Y., Hanamoto, K., Hashiyama, T., Sekine, Y., Takeda, M., Ono, Y. and Tsuzurahara, K.: Antiallergic agents. 3. N-(1H-tetrazol-5-yl)-2-pyridinecarboxamides. J. Med. Chem. 27, 125-128 (1984)
4 Tsuzurahara, K., Ono, Y., Ogiwara, K., Murata, T. and Takeyama, S.: Antiallergic effects of the adrenergic β-stimulant trimetoquinol in rats and guinea pigs. Chem. Pharm. Bull. (Tokyo) 27, 1715-1724 (1979)
5 Chemical Society of Japan: Kagaku-Binran, Kisohen, Vol. 2, p. 1313, Maruzen, Tokyo (1966) (in Japanese)
6 Evans, D.P., Marshall, P.W. and Thomson, D.S.: Inhibition of immediate hypersensitivity reactions in the rat by ICI 74,917 and disodium cromoglycate. Tachyphylaxis and cross-reactivity in vivo and in vitro. Int. Arch. Allergy Appl. Immunol. 49, 417-427 (1975)
7 El-Azab, J. and Stewart, P.B.: The difference in effect of predosing with antiallergic compounds between the rat PCA model and the monkey asthma model. Comparison of the effects of PRD-92-Ea and disodium cromoglycate. Int. Arch. Allergy Appl. Immunol. 55, 343-349 (1977)
8 Goto, K., Terasawa, M., Komori, A. and Maruyama, Y.: Effect of predosing with Y-12,141 on its antiallergic activity.—Studies on antiallergic agents (IV). Folia Pharmacol. Japon. 77, 123-129 (1981) (Abs. in English)
9 Marshall, P.W., Thomson, D.S. and Evans, D.P.: The mechanism of tachyphylaxis to ICI 74,917 and disodium cromoglycate. Int. Arch. Allergy Appl. Immunol. 51, 274-283 (1976)
10 Sung, C.P., Saunders, H.L., Krell, R.D. and Chakrin, L.W.: Studies on the mechanism of tachyphylaxis to disodium cromoglycate. Int. Arch. Allergy Appl. Immunol. 55, 374-384 (1977)
11 Sung, C.P., Saunders, H.L., Lenhardt, E. and Chakrin, L.W.: Further studies on the tachyphylaxis to DSCG. The effects of concentration and temperature. Int. Arch. Allergy Appl. Immunol. 55, 385-394 (1977)
12 Saito, Y.: Clinical pharmacological evaluation of a new anti-allergic agent, TA-5707, by skin and nasal provocation tests. Japan. J. Clin. Pharmacol. Ther. 15, 507-516 (1984) (Abs. in English)
13 Cox, J.S.G.: Disodium cromoglycate (FPL 670) ("Intal"): a specific inhibitor of reaginic antibody-antigen mechanisms. Nature 216, 1328-1329 (1967)
14 Garland, L.G.: Effect of cromoglycate on anaphylactic histamine release from rat peritoneal mast cells. Br. J. Pharmacol. 49, 128-130 (1973)
15 Tsuzurahara, K., Murata, T. and Ishikawa, S.: Studies on the mechanism of action of a new orally-potent antiallergic TA-5707. Japan. J. Allergol. 32, 852 (1983) (in Japanese)
16 Tsuzurahara, K., Ikezawa, K., Ono, Y., Murata, T. and Ishikawa, S.: Antiallergic activity of a new pyridinecarboxamide derivative. TA-5707. Japan. J. Pharmacol. 33, Supp. 122P (1983)
17 Assem, E.S.K. and Richter, A.W.: Comparison of in vivo and in vitro inhibition of the anaphylactic mechanism by β-adrenergic stimulants and disodium cromoglycate. Immunology 21, 729-739 (1971)
18 Taylor, W.A., Francis, D.H., Sheldon, D. and Roitt, I.M.: The anti-anaphylactic actions of disodium cromoglycate, theophylline, isoprenaline and prostaglandins. Int. Arch. Allergy Appl. Immunol. 46, 104-120 (1974)
19 Nagai, H., Takizawa, T., Nakatomi, I., Matsura, N. and Koda, A.: Anti-allergic action of glucocorticoids in rats. Japan. J. Pharmacol. 33, 349-355 (1983)
20 Sellstedt, J.H. and Klauber, D.H.: Process for
preparing tetrazole-5-carboxamide derivatives. United States Patent, 4,129,735 (1978)

21 Nakazawa, M., Yoshimura, T., Naito, J. and Azuma, H.: Pharmacological properties of N-(3',4'-dimethoxycinnamoyl) anthranilic acid (N-5'), a new antiatopic agent (3)—Influence on homologous passive cutaneous anaphylaxis mediated by homocytotropic antibody. Folia Pharmacol. Japon. 74, 467–472 (1978) (Abs. in English)

22 Goto, K., Terasawa, M. and Maruyama, Y.: Anti-allergic activities of a new benzopyranopyridine derivative Y-12,141 in rats. Int. Arch. Allergy Appl. Immunol. 59, 13–19 (1979)

23 Ohmori, K., Ishii, H., Hirayama, T., Shuto, K. and Nakamizo, N.: Pharmacological studies on oxatomide (KW-4354): (2) Effect on the experimental models of the type 1-type 4 allergic reactions. Folia Pharmacol. Japon. 80, 261–270 (1982) (Abs. in English)

24 Ohashi, Y., Nakai, Y., Takeichi, N., Maruoka, K., Minowa, Y., Harada, H., Nakata, J., Kihara, S., Ikeoka, H., Koshimo, H., Kuroki, K. and Takano, H.: Protective effect of a pyridinecarboxamide derivative TA-5707 on the nasal provocation. Oto-Rhino-Laryngology Tokyo 27, Supp. 241–249 (1984) (in Japanese)