J. Pharm. Pharmacol. 1987, 39: 819–824
Received February 3, 1987

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Isolated tissue and binding studies of YM-17690, a novel and non-analogous leukotriene agonist

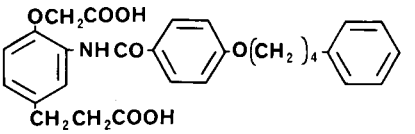
KENICHI TOMIOKA*, TOSHIMITSU YAMADA, KYOKO TERAMURA, MICHIO TERAI†, KAZUYUKI HIDAKA†, TOSHIYASU MASE‡, HIROMU HARA‡ AND KIYOSHI MURASE‡

Departments of Pharmacology, Biochemistry† and Chemistry‡, Central Research Laboratories, Yamanouchi Pharmaceutical Co., Ltd, 1-1-8, Azusawa, Itabashi-ku, Tokyo 174, Japan

YM-17690, 3-[4-carboxymethoxy-3-[*p*-(4-phenylbutoxy)benzamido]phenyl]propionic acid, produced a dose-dependent contraction of guinea-pig ileum and its EC50 value was $1{\cdot}6 \times 10^{-8}$ M. The response was not affected by pretreatment with atropine, mepyramine, indomethacin, dazoxiben and AA-861 (a 5-lipoxygenase inhibitor), but was inhibited by FPL-55712 (an LTD_4 and LTE_4 antagonist). YM-17690 induced dose-dependent contractions of guinea-pig lung parenchyma and trachea with EC50 values of $3{\cdot}9 \times 10^{-9}$ and $2{\cdot}2 \times 10^{-8}$ M, respectively. Pretreatment of these tissues with FPL-55712 resulted in a parallel shift of the YM-17690 dose-response curves to the right. The pA_2 values for FPL-55712 in lung parenchyma and trachea were 7·41 and 8·21, respectively, and the slopes of the regression lines of Schild plots were 1·00 and 1·02, respectively. YM-17690 produced a dose-dependent inhibition of [^{3}H]LTD_4 binding to guinea-pig lung membranes and its pK_i value was 9·28. However, the compound showed only 25% inhibition of [^{3}H]TLC_4 binding to guinea-pig hippocampus membranes, even at 10^{-5} M. These results suggest that YM-17690 is a selective leukotriene (LTD_4 and LTE_4) agonist and that it will therefore be a valuable tool in the study of actions of leukotrienes and for the characterization of their receptors.

Slow reacting substance of anaphylaxis (SRS-A) is comprised of three leukotriene (LT) constituents LTC_4, LTD_4 and LTE_4 (Murphy et al 1979; Örning et al 1980; Lewis et al 1980). It has been suggested that LTs have pathological roles in asthma, other types of immediate hypersensitivity reactions, inflammation, ischaemic heart diseases and psoriasis (Samuelsson 1983; Piper 1984; Ford-Hutchinson 1985). The potential involvement of SRS-A or LTs in these diseases has prompted us to develop agents to inhibit their formation or action. Consequently, several kinds of LT antagonist such as the acetophenone type (Augstein et al 1973; Fleisch et al 1985; O'Donnell et al 1985; Jones et al 1986; Tomioka et al 1986), benzamide type (Toda et al 1985), dithioacetal type (Perchonock et al 1986) and others (Musser et al 1986; Snyder et al 1986) have been reported. We have found that some benzamide derivatives show LT agonist activity and to our knowledge this is the first demonstration of compounds having LT agonist activity, other than LT analogues (Drazen et al 1981; Lewis et al 1981; Okuyama et al 1982).

We now report the in-vitro pharmacological properties of 3-(4-carboxymethoxy-3-[*p*-(4-phenylbutoxy)benzamido]phenyl)propionic acid (YM-17690) (I), one of the most potent of these benzamides.



I
Chemical structure of YM-17690.

MATERIALS AND METHODS

Isolated smooth muscle preparations

The preparations used were: guinea-pig ileum, guinea-pig lung parenchyma prepared according to Lulich et al (1976), and guinea-pig trachea prepared according to Constantine (1965). Preparations were suspended with 1·0 g tension in an organ bath containing 10 mL Tyrode solution equilibrated with a mixture of 95% O_2 and 5% CO_2 at 37 °C. The tissues were equilibrated for 90 min during which the Tyrode solution was replaced every 30 min and the loading tension adjusted to 1 g. The developed tension of the tissue was measured isometrically with a strain gauge transducer (SB-1T, Nihon Kohden), and recorded on a Recticorder (RJG-4008, Nihon Kohden) through a carrier amplifier (RP-5, Nihon Kohden). The tissues were exposed to cumulative concentrations (Van Rossum 1963) of the agonist; antagonist was added 20 min before the first dose of agonist. Specific details of the methods are given in

* Correspondence.

the legends of the Figures and Tables. The EC50 values (the molar concentrations of agonists required to induce 50% of maximal response) were calculated by the Probit method. The dose ratio was obtained from the ratio of an EC50 value of agonist in the presence and in the absence of an antagonist. Antagonist dissociation constants (K_B) were determined at each concentration of the antagonist according to the method of Furchgott (1972). The pA_2 values are then expressed as the negative logarithm of K_B. In addition, the log (dose ratio-1) was plotted against the log of the molar concentration of the antagonist and the regression line and slope of the curve were calculated (Arunlakshana & Schild 1959).

Guinea-pig lung and hippocampus membrane preparations

Male Hartley guinea-pigs, 500 to 600 g, were decapitated and the lungs or hippocampi were removed and chilled in ice-cold 0·9% NaCl.

The lung membrane preparation was prepared according to Mong et al (1984, 1986). The lungs were minced and then homogenized with a motor-driven Teflon homogenizer in 9 volumes of buffer containing 0·25 M sucrose, 2 mM EDTA, 10 μg mL^{-1} soybean trypsin inhibitor, 10 μM phenylmethylsulphonyl fluoride, 100 μg mL^{-1} bacitracin, 10 mM Tris-HCl (pH 7·5). The homogenate was centrifuged at 1000*g* for 10 min at 4 °C and then the supernatant was centrifuged at 32 000*g* for 20 min at 4 °C. The pellet was washed twice with 20 mM Tris-HCl buffer, pH 7·5 suspended in 20 mM Tris-HCl buffer, pH 7·5 and stored at −80 °C.

The hippocampus membrane was prepared as described by Terai et al (1983). The hippocampi were homogenized in 9 volumes of 0·32 M sucrose. The homogenate was centrifuged at 900*g* for 10 min at 4 °C and the pellet was washed once with 0·32 M sucrose. The combined supernatant was further centrifuged at 12 000*g* for 20 min at 4 °C. The pellet was washed twice with 50 mM Tris-HCl buffer, pH 7·5, and was finally suspended in 50 mM Tris-HCl buffer, pH 7·5 and stored at −80 °C.

[^{3}H]LTD_4 and [^{3}H]LTC_4 binding to membranes

[^{3}H]LTD_4 binding to guinea-pig lung membrane preparation. The incubation mixture contained 0·4 nM [^{3}H]LTD_4 in the presence or absence of unlabelled LTD_4 or test compounds and guinea-pig lung membrane protein (200 μg mL^{-1}) in a volume of 1 mL incubation buffer containing 10 mM $MgCl_2$, 10 mM $CaCl_2$, 1 mM cysteine, 1 mM glycine and 10 mM HEPES-Tris (pH 6·5). The mixture was incubated for 30 min at 25 °C under argon in the dark.

[^{3}H]LTC_4 binding to guinea-pig hippocampus membranes. The incubation mixture contained 1 nM [^{3}H]LTC_4 in the presence or absence of unlabelled LTC_4, or test compounds, and hippocampus membrane protein (200 μg mL^{-1}) in a volume of 1 mL incubation buffer containing 10 nM $MgCl_2$, 10 mM $CaCl_2$, 1 mM cysteine, 1 mM glycine, 20 mM serine-borate and 10 mM HEPES-Tris (pH 6·5). The incubation mixture was incubated for 30 min at 25 °C under argon in the dark.

Free ligand was separated from membrane-bound ligand by vacuum filtration through Whatman GF/B glass fibre filters and by washing with 20 mL of incubation buffer. The radioactivity on the filter was counted with a Packard Tricarb liquid scintillation spectrometer. Total and non-specific binding values were defined as the [^{3}H]LTD_4 or [^{3}H]LTC_4 bound to the membranes in the absence or presence of 1 μM LTD_4 or LTC_4, respectively. The specific binding was defined as that amount of [^{3}H]LTD_4 or [^{3}H]LTC_4 bound to the membrane when the non-specific component was subtracted from the total binding.

The radioligand competition activity (K_i) of each compound was calculated from the equation: $K_i = IC50/(1 + [[^3H]LTs]/K_d)$ where IC50 is the concentration required to inhibit specific binding by 50% and K_d is the dissociation constant of radioligand. The pK_i values were calculated from the negative logarithm of K_i values.

Drugs

YM-17690, dazoxiben and AA-861 were synthesized in these laboratories. The following drugs were purchased: LTD_4 (Wako), LTC_4 (Wako), [^{3}H]LTD_4 (39·0 Ci $mmol^{-1}$; New England Nuclear), [^{3}H]LTC_4 (39·0 Ci $mmol^{-1}$; New England Nuclear), histamine dihydrochloride (Sigma), acetylcholine hydrochloride (Daiichi), carbamylcholine chloride (Sigma), mepyramine maleate (Sigma), atropine sulphate (Tanabe), indomethacin (Sumitomo), soybean trypsin inhibitor (Sigma), phenylmethylsulphonyl fluoride (Nakarai), bacitracin (Sigma), cysteine (Wako) and glycine (Wako). FPL-55712 was a gift from Fisons.

RESULTS

Isolated tissue study

Guinea-pig ileum. LTD_4 and YM-17690 produced a dose-dependent contraction of ileum (Fig. 1A) and

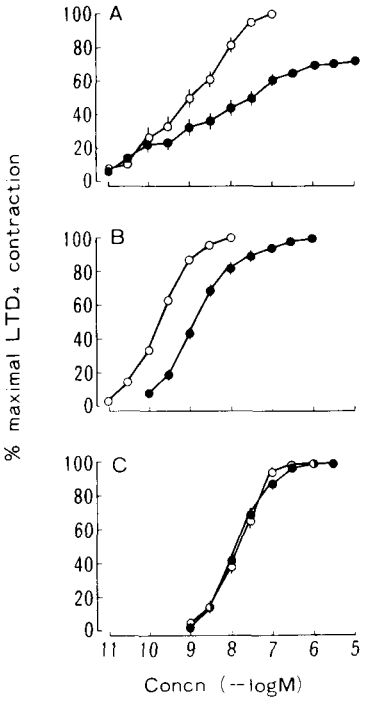


FIG. 1. Contractile effects of LTD_4 (—○—) and YM-17690 (—●—) on guinea-pig ileum (A), lung parenchyma (B) and trachea (C). To minimize intertissue variability, the contractions induced by LTD_4 and YM-17690 were standardized as a per cent of the contraction elicited by the reference standards (10^{-6} M acetylcholine on the ileum, 10^{-4} M histamine on the lung parenchyma and 10^{-4} M carbachol on the trachea added 1 h before obtaining the dose-response curve). Under these conditions the maximal response induced by YM-17690 on the ileum, lung parenchyma and trachea was 72, 100 and 100%, respectively, of that induced by LTD_4. The results represent the mean ± s.e.m. of 16 to 34 preparations.

Table 1. Contractile activities of LTD_4 and YM-17690 in guinea-pig ileum, lung parenchyma and trachea.

Tissue	EC50 (M) LTD_4	EC50 (M) YM-17690
Ileum	$(1.5 \pm 0.3) \times 10^{-9}$ (16)	$(1.6 \pm 1.0) \times 10^{-8}$ (16)
Lung	$(2.1 \pm 0.2) \times 10^{-10}$ (34)	$(3.9 \pm 1.5) \times 10^{-9}$ (29)
Trachea	$(1.9 \pm 0.4) \times 10^{-8}$ (21)	$(2.2 \pm 0.4) \times 10^{-8}$ (27)

The values are the mean ± s.e.m. for the number of preparations indicated in parentheses.

their EC50 values were 1.5×10^{-9} and 1.6×10^{-8} M, respectively (Table 1). The maximal response induced by YM-17690 was 72% of that induced by LTD_4. In an attempt to see whether contraction induced by YM-17690 of the ileum is mediated through cholinergic, histaminergic and leukotriene receptors, or cyclooxygenase and lipoxygenase products, we investigated the effects of corresponding antagonists and enzyme inhibitors on the contraction. As shown in Table 2, neither atropine (3×10^{-7} M), mepyramine (10^{-6} M), indomethacin (10^{-6} M), dazoxiben (10^{-4} M) nor AA-861 (3×10^{-7} M) altered the contractile response of the ileum to YM-17690. On the other hand, FPL-55712 (3×10^{-7} M) shifted the YM-17690 dose-response curve to the right without depressing the maximal response (Table 2).

Table 2. Effects of atropine (3×10^{-7} M), mepyramine (10^{-6} M), indomethacin (10^{-6} M), dazoxiben (10^{-4} M), AA-861 (3×10^{-7} M) and FPL-55712 (3×10^{-7} M) on YM-17690-induced contraction of guinea-pig ileum.

Compound	n	YM-17690 (EC50 M) Control[a]	YM-17690 (EC50 M) Antagonist[a]	Significance P
Atropine	9	$(4.1 \pm 1.3) \times 10^{-9}$	$(9.1 \pm 2.6) \times 10^{-9}$	N.S.[b]
Mepyramine	9	$(2.2 \pm 1.0) \times 10^{-8}$	$(2.7 \pm 1.8) \times 10^{-8}$	N.S.
Indomethacin	4	$(9.7 \pm 3.7) \times 10^{-9}$	$(8.0 \pm 0.9) \times 10^{-9}$	N.S.
Dazoxiben	7	$(2.3 \pm 0.9) \times 10^{-8}$	$(2.8 \pm 1.4) \times 10^{-8}$	N.S.
AA-861	4	$(7.4 \pm 1.1) \times 10^{-9}$	$(7.2 \pm 2.8) \times 10^{-9}$	N.S.
FPL-55712	4	$(2.0 \pm 0.8) \times 10^{-8}$	$(2.4 \pm 0.6) \times 10^{-7}$	<0.05

The values are the mean ± s.e.m. for the indicated number of preparations.

All antagonists used did not alter the maximal response of guinea-pig ileum to YM-17690 as estimated by the relative contraction to 10^{-6} M acetylcholine added 1 h before obtaining the dose-response curve. [a] Two preparations of ileum were taken from each animal. One preparation was subjected to antagonist and another one was control (vehicle). [b] Not significant by paired *t*-test ($P > 0.05$).

Guinea-pig lung parenchyma. LTD_4 and YM-17690 caused a dose-dependent contraction (Fig. 1B) and their EC50 values were 2.1×10^{-10} and 3.9×10^{-9} M, respectively (Table 1). YM-17690 achieved the same maximal response as LTD_4 (Fig. 1B). To determine whether YM-17690-induced contraction of lung parenchyma is mediated by LT receptors, we examined the effect of FPL-55712 pretreatment. As shown in Fig. 2, FPL-55712 at 10^{-7} to 10^{-5} M produced a parallel shift of the YM-17690 dose-response curves to the right without attenuation of the maximal response. The pA_2 value for FPL-55712 and its slope of regression line of Schild plots were 7.41 and 1.00, respectively (Table 3).

Guinea-pig trachea. LTD_4 and YM-17690 produced a dose-dependent contraction with the same maximal responses (Fig. 1C) and their EC50 values were 1.9×10^{-8} and 2.2×10^{-8} M, respectively (Table 1). FPL-55712 at 3×10^{-8} to 3×10^{-7} M shifted the

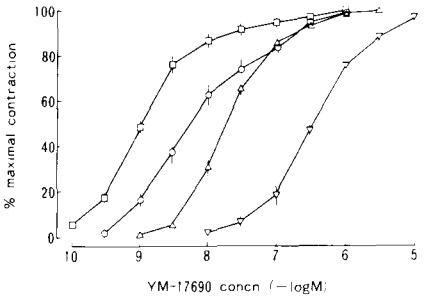


FIG. 2. Contractile response of guinea-pig lung parenchyma to YM-17690 in the absence (—□—) and presence of FPL-55712 (10^{-7} M, —○—), (10^{-6} M, —△—) and (10^{-5} M, —▽—). Two preparations of lung parenchyma were taken from each animal. One was subjected to antagonist and the other was control (vehicle). FPL-55712 did not alter the maximal response of lung parenchyma to YM-17690 as estimated by the relative contraction to 10^{-4} M histamine added 1 h before obtaining the dose-response curve. The results represents the mean ± s.e.m. of 4 to 14 preparations.

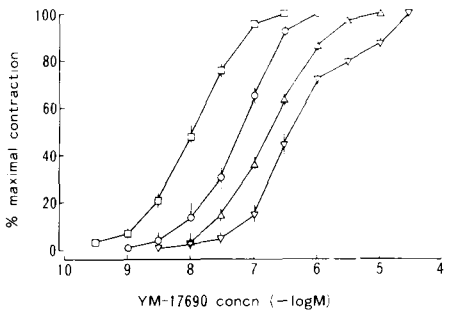


FIG. 3. Contractile response of guinea-pig trachea to YM-17690 in the absence (—□—) and presence of FPL-55712 (3×10^{-8} M, —○—), (10^{-7} M, —△—) and (3×10^{-7} M, —▽—). Trachea obtained from each animal was halved. One preparation was subjected to antagonist and the other was control (vehicle). FPL-55712 did not alter the maximal response of trachea to YM-17690 as estimated by the relative contraction to 10^{-4} M carbachol added 1 h before obtaining the dose-response curve. The results represent the mean ± s.e.m. of 4 to 14 preparations.

Table 3. pA_2 values and the slopes of Schild plots for FPL-55712 in guinea-pig lung parenchyma and trachea with YM-17690 as agonist.

Tissue	n	pA_2	Slope
Lung	14	7·41 ± 0·07	1·00 (0·81–1·20)
Trachea	14	8·21 ± 0·06	1·02 (0·67–1·38)

The values are the mean ± s.e.m. or the mean with 95% confidence limits in parentheses for the indicated number of preparations.

YM-17690 dose-response curves in a parallel manner without reduction of the maximal response (Fig. 3). The pA_2 value for FPL-55712 and its slope of regression line of Schild plots were 8·21 and 1·02, respectively (Table 3).

Radioligand binding study

[^{3}H]LTD$_4$ binding. The dissociation constant (K_d) and maximum number of binding sites (B_{max}) for [^{3}H]LTD$_4$ binding to guinea-pig lung membranes were obtained from the Scatchard plot (Scatchard 1949) of the specific binding at the concentrations between 0·5 and 3·8 nM. Their values were 0·15 ± 0·01 nM and 429 ± 12 fmol mg^{-1} protein, respectively, and were comparable with the values reported by Mong et al (1986). LTD_4, YM-17690 and FPL-55712 produced a dose-dependent inhibition of [^{3}H]LTD$_4$ binding to guinea-pig lung membranes (Fig. 4). The pK_i values of LTD_4, YM-17690 and FPL-55712 were 9·79, 9·28 and 6·10, respectively

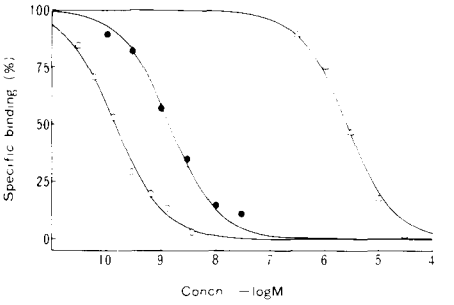


FIG. 4. The inhibition of [^{3}H]LTD$_4$ binding to guinea-pig lung membranes by YM-17690 and FPL-55712. The abscissa indicates −log concentration of the drugs, and the ordinate indicates per cent of specific binding of [^{3}H]LTD$_4$. Inhibition of the binding by YM-17690 (—●—) and FPL-55712 (—△—) were determined with the concentration of 0·4 nM [^{3}H]LTD$_4$. The dose binding of LTD_4 (—○—) in the Scatchard analysis is superimposed on the Fig. (the ordinate indicates per cent of remaining high affinity sites). Each point is the mean ± s.e.m. of 3 to 8 experiments.

(Table 4). The Hill coefficients for these compounds were near to 1·0 (Table 4), suggesting that these agents competed with [^{3}H]LTD$_4$ at its high affinity binding sites.

[^{3}H]LTC$_4$ binding. LTC_4 produced a dose-dependent inhibition of [^{3}H]LTC$_4$ binding to guinea-pig hippocampus membranes (Fig. 5) and its IC50 value was $5·5 \times 10^{-8}$ M. On the other hand, YM-17690 and LTD_4 at 10^{-5} M showed only 25 and 40% inhibition, respectively, of [^{3}H]LTC$_4$ binding to hippocampus membranes. FPL-55712 did not affect [^{3}H]LTC$_4$

Table 4. Inhibition of [^{3}H]LTD_4 binding sites by LTD_4, YM-17690 and FPL-55712 in the guinea-pig lung membranes.

Compound	n	pK_i	Hill coefficient
LTD_4	3	9·79 ± 0·08	0·86 (0·75–0·97)
YM-17690	8	9·28 ± 0·02	0·87 (0·76–0·97)
FPL-55712	6	6·10 ± 0·01	1·22 (1·14–1·31)

The values are the mean ± s.e.m. or the mean with 95% confidence limits in parentheses for the indicated number of experiments.

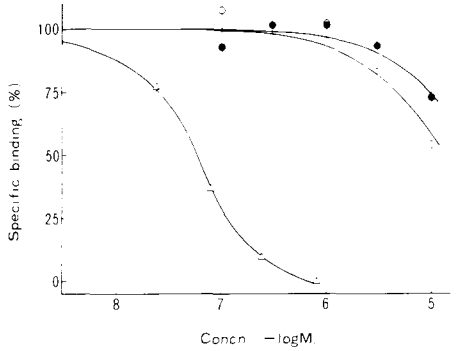


FIG. 5. The inhibition of [^{3}H]LTC_4 binding to guinea-pig hippocampus membranes by LTC_4, LTD_4 and YM-17690. The abscissa indicates −log concentration of the drugs, and the ordinate indicates per cent of specific binding of [^{3}H]LTC_4. Inhibition of the binding by LTC_4 (—△—), LTD_4 (—○—) and YM-17690 (—●—) were determined with the concentration of 1 nM [^{3}H]LTC_4. Each point is the mean ± s.e.m. of 3 to 6 experiments.

binding even in doses up to 3×10^{-5} M (data not shown).

DISCUSSION

A novel benzamide derivative, YM-17690, produced dose-dependent contractions of guinea-pig ileum, lung parenchyma and trachea. The contractile response of the ileum to YM-17690 was not affected by pretreatment with atropine, mepyramine, indomethacin, dazoxiben (a thromboxane synthetase inhibitor, Randall et al 1981) or AA-861 (Yoshimoto et al 1982) (Table 2). These results suggest that neither the cholinergic and histaminergic mechanisms nor cyclooxygenase and lipoxygenase products are involved in this contractile response. On the other hand, FPL-55712, an LTD_4 and LTE_4 antagonist (Snyder & Krell 1984), significantly inhibited YM-17690-induced contraction of guinea-pig ileum (Table 2). Furthermore, pretreatment of guinea-pig lung parenchyma and trachea with FPL-55712 resulted in a parallel shift of the YM-17690 dose-response curves to the right (Figs 2, 3). Competitive antagonism of FPL-55712 against YM-17690-induced contraction of the guinea-pig lung parenchyma and trachea was confirmed by the slope of unity of the Schild plot (Table 3). YM-17690, therefore, appears to be a selective LT agonist. Its contractile activity was equal to that of LTD_4 in trachea but 10-fold less than that of LTD_4 in ileum and lung parenchyma (Table 1). It is reported that L-cysteine, an aminopeptidase inhibitor, shifted the LTD_4 dose-response curve to the left in guinea-pig trachea due to the inhibition of LTD_4 bioconversion to less active LTE_4 (Snyder et al 1984). Thus, real contractile activity of LTD_4 in trachea appears to be more potent than that of YM-17690. YM-17690 achieved the same maximal response as LTD_4 in guinea-pig lung parenchyma and trachea but the maximal response relative to LTD_4 was only 72% in ileum (Fig. 1), indicating that YM-17690 acts as a full agonist in guinea-pig airway tissues whereas it was a partial agonist in ileum. Our results thus obtained suggest that there are different LTD_4 receptors in guinea-pig airways and ileum as proposed by Fleisch et al (1982).

To characterize further the LT agonist action of YM-17690, we investigated the effect of YM-17690 on [^{3}H]LTD_4 and [^{3}H]LTC_4 binding using guinea-pig lung and hippocampus membranes. YM-17690 and LTD_4 produced a dose-dependent inhibition of [^{3}H]LTD_4 binding to the lung membranes (Fig. 4). The order of potency of these compounds correlated with their contractile effect in lung parenchyma. On the other hand, YM-17690 and LTD_4 at 10^{-5} M showed only 25 to 40% inhibition of [^{3}H]LTC_4 binding to hippocampus membranes (Fig. 5). FPL-55712 had no effect against [^{3}H]LTC_4 binding to hippocampus membranes at concentrations that were effective against [^{3}H]LTD_4 binding to lung membranes. Such a selective inhibition of [^{3}H]LTD_4 binding by LTD_4 and FPL-55712 has already been reported by Mong et al (1985a). These results clearly indicate that YM-17690 specifically acts on LTD_4 receptors as in the cases of LTD_4 and FPL-55712. However, whether YM-17690 is a selective LTD_4 agonist or LTD_4/LTE_4 agonist has yet to be resolved, since the induction of contraction in guinea-pig lung parenchyma by LTD_4 and LTE_4 is mediated by the same receptor and via similar mechanisms (Mong et al 1985b).

In conclusion, our results indicate that YM-17690 is a novel and non-analogous LT (LTD_4 and LTE_4)

agonist. Therefore, YM-17690 will be a valuable tool for the study of the actions of LTs and for the characterization of LT receptors. In addition, it is synthetized easily and has the advantage of being stable and crystalline in comparison with natural LTs.

Acknowledgements

The authors wish to thank Drs H. Maeno, N. Inukai, H. Nagano, M. Takeda and G. Kon for their encouragement throughout this work and Miss T. Hanazato for her excellent technical assistance. We are also grateful to Fisons Ltd for supplying FPL-55712.

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