A Novel Dual Antagonist of Thromboxane A\(_2\) and Leukotriene D\(_4\) Receptors: Synthesis and Structure–Activity Relationships of Chloroquinolylvinyl Derivatives

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To discover an orally active thromboxane A\(_2\) (TXA\(_2\)) and leukotriene D\(_4\) (LTD\(_4\)) dual antagonist, we designed and synthesized chloroquinolylvinyl derivatives based on the structures of the TXA\(_2\) antagonist daltroban and the LTD\(_4\) antagonist montelukast. Among these derivatives, 4-[[((2-(4-chlorophenylsulfonylamino)-1-{3-[[((E)-2-(7-chloro-2-quinolyl)vinyl]phenyl]ethyl][thio][methyl]benzoic acid (18d) showed potent inhibitory activity against U46619-induced aggregation of guinea pig platelets and LTD\(_4\)-induced contraction in the guinea pig ileum, with \(IC_{50}\) values of 340 nm and 0.40 nm, respectively. Oral administration of 18d also inhibited both the LTD\(_4\)-induced acceleration of plasma leakage to skin in guinea pig and the U46619-induced increase in airway resistance in guinea pig with \(ED_{50}\) values of 0.47 mg/kg and 3.3 mg/kg, respectively.

Key words leukotriene D\(_4\); thromboxane A\(_2\); dual antagonist; structure–activity relationship

Asthma is regarded as an inflammatory disease of the respiratory tract. Arachidonic acid released from membrane phospholipids by phospholipase A\(_2\) is converted to various metabolites that play important roles in asthma\(^{2,3}\): thromboxane A\(_2\) (TXA\(_2\)) is produced from arachidonic acid through the cyclooxygenase pathway and leukotrienes (LTs) are synthesized through the 5-lipoxygenase pathway. TXA\(_2\) and LTD\(_4\) are considered to be aggravating factors in asthma with TXA\(_2\) inducing bronchial hyperreactivity and bronchoconstriction,\(^{3,4}\) and LTD\(_4\) inducing potent bronchoconstriction, enhanced vascular permeability and mucus secretion.\(^{5,6}\) In addition, the levels of TXA\(_2\) and LTs in the plasma, bronchoalveolar lavage fluid (BALF) and urine from patients with bronchial asthma have been shown to be elevated.\(^{7}\) Based on these observations, TXA\(_2\) and LTD\(_4\) are thought to be potential targets for anti-asthmatic drugs: in fact, highly potent and selective antagonists for these mediators have been used for treatment of asthma.\(^{8–10}\) However, TXA\(_2\) and LTD\(_4\) play different roles in the symptoms of asthma, and clinical trial results of TXA\(_2\) receptor antagonists,\(^{11–13}\) and LTD\(_4\) receptor antagonists\(^{14,15}\) suggest that the predominant mediator varies from patient to patient. These results suggest that an antagonist for both TXA\(_2\) and LTD\(_4\) receptors would be more effective in the treatment of asthma, compared to the selective antagonists. Some TXA\(_2\) and LTD\(_4\) dual receptor antagonists, such as RS-601\(^{16}\) and YM-158,\(^{17–22}\) have been reported to have potent efficacy in various antiasthmatic models.

Based on the above, we planned to design a novel dual antagonist for the TXA\(_2\) and LTD\(_4\) receptors. The potent and selective LTD\(_4\) antagonist montelukast\(^{23}\) contains a lipophilic chloroquinolylvinyl group and a carboxyl group, whereas the potent and selective TXA\(_2\) antagonist daltroban\(^{24}\) is a chlorobenzensulfonamide that also contains a carboxyl group. Since both montelukast and daltroban have a carboxyl group, the TXA\(_2\) and LTD\(_4\) receptor dual antagonists were designed by introducing the chlorobenzensulfonamide group of daltroban into the structure of montelukast (Fig. 1). In this report, we describe the structure–activity relationships of TXA\(_2\) and LTD\(_4\) receptor dual antagonists and the pharmacological profiles of selected inhibitors.

Chemistry A series of the 4-chlorobenzensulfonamide propyl derivatives 7a–h was synthesized using the procedure shown in Chart 1. The allylic alcohol 1 was oxidized by manganese dioxide to afford the \(\alpha,\beta\)-unsaturated ketone 2. Michael addition of chlorobenzenesulfonamide to compound 2 gave the sulfonamide 3, and the carbonyl group of compound 3 was reduced by sodium borohydride to afford the alcohol derivative 4, which was treated with thionyl chloride to give the benzyl chloride 5. Thioalkylation of compound 5 with various thiols gave the esters 6a–h, which were hydrolyzed to afford compounds 7a–h.

A series of benzenesulfonamide ethyl derivatives 18a–j was synthesized using the procedure shown in Chart 2. Condensation of the 7-chloro-2-methylquinoline 8\(^{20}\) and methyl 3-formylbenzoate in the presence of acetic anhydride gave the ester 9, which was hydrolyzed to afford the benzoic acid derivative 10. Compound 10 was reacted with ethyl isocyanoacetate in the presence of diphenylphosphoryl azide (DPPA) to afford the oxazole derivative 11, which was treated with hydrochloric acid to give the aminoketone derivative 12, followed by the reduction with sodium borohydride
to afford the aminoalcohol 13. The amino group of com-

pound 13 was protected with phthalic anhydride, and the re-
sulting phthalimide derivative was treated with methanesul-

donyl chloride to give the mesylate 15, which was reacted

with various thiols to give the sulfides 16a—f. Compounds

16a—f were treated with methylhydrazine, and the resulting

amines were reacted with various sulfonyl chlorides. The re-

sulting esters 17a—j were hydrolyzed to give compounds

18a—j.

Results and Discussion

The inhibitory activities of compounds 7a—h and 18a—j

against U46619-induced aggregation in guinea pig platelets

and against LTD₄-induced contraction in guinea pig ileum
were evaluated, and the results are listed in Table 1.

Among the 4-chlorobenzenesulfonamide propyl derivatives, the compound possessing an acetic acid group on the sulfur atom (7a) showed no TXA2 antagonist activity. Replacement of the acetic acid group (7a) with propanoic acid group (7b) or butanoic acid group (7c) enhanced the TXA2 antagonistic activity, and derivative 7c showed particularly potent TXA2 antagonist activity with an IC50 value of 150 nM. The introduction of 3,3-dimethyl (7d) or dimethylene (7e) groups on the butanoic acid reduced the TXA2 antagonist activity, with IC50 values of 1100 nM and 500 nM, respectively. Replacement of butanoic acid (7c) on the sulfur atom with 4-carboxyphenylmethyl (7f), 4-carboxymethylphenylmethyl (7g) or 2-(4-carboxyphenyl)ethyl (7h) groups reduced the TXA2 inhibitory activity compared with compound 7c. Introduction of a phenyl ring or bulky substituent between the sulfur atom and the carboxylic acid group were unfavorable for TXA2 antagonist activity.

Among the 4-chlorobenzenesulfonamide ethyl derivatives 18a—f, the compounds possessing propanoic acid (18a), 3,3-dimethylbutanoic acid (18b) and 3,3-dimethylenebutanoic acid (18c) on the sulfur atom showed less potent TXA2 antagonist activities than that of daltroban. On the contrary, the compounds with 4-carboxyphenylmethyl (18d) and 2-(4-carboxyphenyl)ethyl (18f) groups on the sulfur atom showed potent TXA2 antagonist activities with IC50 values of 340 nM and 510 nM, respectively. The compound with a 4-carboxymethylphenylmethyl group (18e) on the sulfur atom showed reduced TXA2 antagonist activity, compared with compound 18d. In the 4-chlorobenzencesulfonamide ethyl derivatives, introduction of a phenyl ring on the sulfur atom was favorable for TXA2 antagonist activity.

Next, we investigated the influence of the substituent on the 4-position of the benzene sulfonamide group on TXA2 antagonistic activity. Removal of the chloro group (18g) caused loss of activity. The bromo derivative 18h was almost as potent as the chloro derivative 18d, but the nitro (18i) and fluoro (18j) derivatives showed decreased TXA2 antagonist activity. From these results, it was concluded that the nature of the substituents on the 4-position of the benzene sulfonamide group are important for TXA2 antagonistic activity.

As shown in Table 1, montelukast has potent LTD4 antagonist activity with an IC50 value of 0.085 nM. In the series of 4-chlorobenzencesulfonamide propyl derivatives, the influence of the length of the methylene chain on the sulfur atom (7a—c) on the LTD4 antagonistic activity differed from that for TXA2 antagonistic activity. The compound with a propanoic acid group on the sulfur atom (7b) showed potent LTD4 antagonist activity, with an IC50 value of 0.41 nM. Replacement of the propanoic acid group in compound 7b with acetic acid (7a) or butanoic acid (7c) resulted in a decrease in the LTD4 antagonistic activity. Compounds with dimethyl (7d) or dimethylene (7e) groups at the 3 position of the butanoic acid group in compound 7c retained potent LTD4 antagonist activities, with IC50 values of 0.41 and 0.21 nM, respectively. These results suggest that a bulky substituent at the 3 position of the butanoic acid group in compound 7c is tolerated for LTD4 antagonistic activity. Replacement of the propanoic acid group of compound 7b with 4-carboxyphenylmethyl (7f), 4-carboxymethylphenylmethyl (7g) or 4-carboxyphenylethyl (7h) groups resulted in a decrease in LTD4 antagonist activity suggesting that a phenyl group in this position causes a loss of this activity.

Among the 4-chlorobenzencesulfonamide ethyl derivatives, the compound with a 2-propanoic acid group (18a) on the sulfur atom showed LTD4 antagonist activity, with an IC50 value of 1.7 nM. Replacement of the carboxyethyl group in compound 18a with 3,3-dimethylenebutanoic acid (18b) or 3,3-dimethylenebutanoic acid (18c) groups on the sulfur atom increased the LTD4 antagonist activity, with IC50 values of 0.24 nM and 0.23 nM, respectively. These results suggest that bulky substituents on the butanoic acid in compound 18a are favorable for LTD4 antagonist activity. Replacement of the propanoic acid group in compound 18a with a carboxyphenylmethyl group (18d) resulted in an increase in this activity, with an IC50 value of 0.40 nM. The compounds with carboxyphenylmethyl (18e) or carboxyphenylethyl

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### Table 1. TXA2 and LTD4 Antagonist Activities of Chloroquinolylvinyl Derivatives

<table>
<thead>
<tr>
<th>No.</th>
<th>R</th>
<th>IC50 (nM)</th>
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<tr>
<td></td>
<td></td>
<td>TXA2</td>
</tr>
<tr>
<td>7a</td>
<td>CO₂H</td>
<td>51000</td>
</tr>
<tr>
<td>7b</td>
<td>CO₂H</td>
<td>1000</td>
</tr>
<tr>
<td>7c</td>
<td>CO₂H</td>
<td>150</td>
</tr>
<tr>
<td>7d</td>
<td>CO₂H</td>
<td>1100</td>
</tr>
<tr>
<td>7e</td>
<td>CO₂H</td>
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<td>7f</td>
<td>CO₂H</td>
<td>980</td>
</tr>
<tr>
<td>7g</td>
<td>CO₂H</td>
<td>4400</td>
</tr>
<tr>
<td>7h</td>
<td>CO₂H</td>
<td>1000</td>
</tr>
<tr>
<td>18a</td>
<td>Me</td>
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<td>18c</td>
<td>Me</td>
<td>1400</td>
</tr>
<tr>
<td>18d</td>
<td>Me</td>
<td>340</td>
</tr>
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<td>CO₂H</td>
<td>1100</td>
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<tr>
<td>18f</td>
<td>Cl</td>
<td>510</td>
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<tr>
<td>18g</td>
<td>H</td>
<td>680</td>
</tr>
<tr>
<td>18h</td>
<td>Br</td>
<td>500</td>
</tr>
<tr>
<td>18i</td>
<td>NO₂</td>
<td>1000</td>
</tr>
<tr>
<td>18j</td>
<td>F</td>
<td>750</td>
</tr>
<tr>
<td></td>
<td>Montelukast</td>
<td>N.D.</td>
</tr>
</tbody>
</table>

a) Not determined.
(18f) groups showed less potent LTD₄ antagonist activity compared to compound 18d, with IC₅₀ values of 2.1 nm and 3.0 nm, respectively. These results suggest that the distance between the sulfur atom and the carboxylic acid group is important for potent LTD₄ antagonist activity.

Removal (18g) or replacement of the chloro group at the 4-position of the benzenesulfonamide group in compound 18d with bromo (18h), nitro (18i) or fluoro (18j) groups increased the LTD₄ antagonist activity, with IC₅₀ values of 0.41 nm, 0.077 nm, 0.23 nm and 0.12 nm, respectively. These results suggest that substituents on the benzenesulfonamide group do not significantly influence the activity.

Selected compounds (7c, 17e, 18d, 18g, 18h, 18j) which possessed potent TXA₂ and LTD₄ antagonist activities were tested for their ability to inhibit the LTD₄-induced acceleration of plasma leakage to skin and U46619-induced increase in airway resistance in guinea pig after oral administration. The results are shown in Table 2. Compounds 17e and 18d showed potent inhibition of LTD₄-induced acceleration of plasma leakage, with ED₅₀ values of 0.12 and 0.47 mg/kg, respectively. Compound 18d also showed inhibitory activity against the U46619-induced increase in airway resistance with an ED₅₀ value of 3.3 mg/kg. Compound 17e was less potent than compound 18d in this respect.

In conclusion, in order to find an orally active TXA₂ and LTD₄ dual antagonist, we designed and synthesized chloroquinolylinylphenyl derivatives based on the molecular structures of the TXA₂ antagonist daltroban and the LTD₄ antagonist montelukast. Among these compounds, 18d showed potent TXA₂ and LTD₄ antagonist activity both in vitro and in vivo.

Experimental

H-NMR spectra were obtained on a JEOL JNM-EX90 or JNM-A500 spectrometer and chemical shifts are expressed as δ (ppm) values with tetramethylsilane as the internal standard. Abbreviations of the 1H-NMR signal patterns are as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; m, multiplet; br, broad. Mass spectra were obtained on a JEOL JMS-DX300 or Hitachi M-80 spectrometer. Column chromatography on silica gel was performed with Wakogel C-200. Preparative thin-layer chromatography was performed with Merck PLC plate Silica gel 60 F₂₅₄. Column chromatography of the residue on silica gel (AcOEt:CHCl₃;

Table 2. Inhibitory Activities of U46619-Induced Increase in Airway Resistance in Guinea Pig and LTD₄-Induced Acceleration of Plasma Leakage in Guinea Pig Skin

<table>
<thead>
<tr>
<th>No.</th>
<th>U46619-induced airway resistance ED₅₀ (mg/kg)</th>
<th>LTD₄-induced plasma leakage ED₅₀ (mg/kg)</th>
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</thead>
<tbody>
<tr>
<td>7c</td>
<td>N.D.²⁴</td>
<td>54%²⁴</td>
</tr>
<tr>
<td>7e</td>
<td>38%²⁴</td>
<td>12.1</td>
</tr>
<tr>
<td>18d</td>
<td>3.3</td>
<td>0.47</td>
</tr>
<tr>
<td>18g</td>
<td>N.D.²⁴</td>
<td>63%²⁴</td>
</tr>
<tr>
<td>18h</td>
<td>N.D.²⁴</td>
<td>24%²⁴</td>
</tr>
<tr>
<td>18j</td>
<td>N.D.²⁴</td>
<td>44%²⁴</td>
</tr>
</tbody>
</table>

n-hexane=3:30:70 gave 2 (10.6 g, 41%) as a colorless solid. 1H-NMR (CDCl₃): 5.97 (1H, dd, J=10.8, 1.6 Hz), 6.48 (1H, dd, J=17.2, 1.6 Hz), 7.18 (1H, dd, J=17.2, 10.8 Hz), 7.37—7.44 (2H, m), 7.50 (1H, t, J=6.7 Hz, 7.59 (1H, d, J=8.4 Hz), 7.69 (1H, d, J=8.4 Hz), 7.73 (1H, d, J=16.8 Hz), 7.80 (1H, d, J=7.6 Hz), 7.88 (1H, d, J=7.6 Hz, 8.05—8.09 (2H, m), 8.18 (1H, s). FAB-MS m/z: 320 [M+H]⁺.

4-Chloro-N-[3-[[E]-2-(7-chloro-2-quinolyl)vinyl]phenyl]-3-oxopropanesulfonamide (3) A mixture of 2 (8.70 g, 27.2 mmol), 4-chlorobenzenesulfonamide (5.73 g, 29.9 mmol), potassium tert-butoxide (10.0 g, 0.89 mmol), 1,4-dioxane (80 ml) and benzene (80 ml) was stirred at 80°C for 10 h. The reaction mixture was washed with water, and then filtered through celite. The filtrate was evaporated in vacuo. Column chromatography of the residue on silica gel (0.2% MeOH–CHCl₃) gave 3 as a yellow amorphous solid. 1H-NMR (CDCl₃): 2.24—2.31 (2H, m), 3.07—3.25 (2H, m), 3.29 (2H, br t, J=6.0 Hz), 3.90—3.98 (2H, m), 4.86 (1H, t, J=8.4 Hz), 5.65 (1H, br t, J=5.8 Hz), 7.16 (1H, br d, J=10.8 Hz), 7.26—7.31 (2H, m), 7.37 (1H, d, J=8.8 Hz), 7.44 (1H, d, J=8.8 Hz), 7.57—7.62 (2H, m), 7.68 (2H, d, J=8.8 Hz), 8.79 (2H, d, J=8.0 Hz), 7.99 (1H, brd, J=1.6 Hz), 8.07 (1H, d, J=8.8 Hz). FAB-MS m/z: 513 [M+H]⁺.

4-Chloro-N-[3-[[E]-2-(7-chloro-2-quinolyl)vinyl]phenyl]-3-hydroxypropanesulfonamide (4) A mixture of 3 (8.40 g, 16.4 mmol) in 1,2-dichloroethane was combined with thionyl chloride (1.43 ml, 19.6 mmol) at 5°C. The reaction mixture was stirred at room temperature for 5 h, and then ice and saturated aqueous sodium bicarbonate solution were added. The reaction mixture was extracted with CHCl₃, washed with brine, dried over Na₂SO₄, and evaporated in vacuo. Column chromatography of the residue on silica gel (AcOEt:n-hexane=1:4:3:7) gave 4 as a colorless solid. 1H-NMR (CDCl₃): 2.00—2.06 (2H, m), 2.47—2.64 (4H, m), 3.03—3.08 (2H, m), 3.68 (3H, s), 3.90 (1H, t, J=6.6 Hz), 4.91 (1H, t, J=6.4 Hz), 7.19—7.80 (13H, m), 8.08—8.13 (2H, m). FAB-MS m/z: 615 [M+H]⁺.

Methyl 4-[3-[4-(Chlorophenylsulfonyl)amino]-1-[3-[[E]-2-(7-chloro-2-quinolyl)vinyl]phenyl]propyl]thioacetate (6a). A mixture of 5 (0.50 g, 0.9 mmol) in MeOH-dimethylsulfoxide-d₆ was combined with cesium carbonate (1.61 g, 1.9 mmol) and methyl 3-mercaptopropionate (0.17 g, 1.4 mmol) at 10°C. The reaction mixture was stirred at 40°C for 12 h, water was added, the reaction mixture was extracted with ethyl acetate, washed with water and brine, dried over MgSO₄, and evaporated in vacuo. Column chromatography of the residue on silica gel (AcOEt:n-hexane=1:3) gave 6b as a yellow amorphous solid. 1H-NMR (CDCl₃): 2.00—2.06 (2H, m), 2.47—2.64 (4H, m), 3.03—3.08 (2H, m), 3.68 (3H, s), 3.90 (1H, t, J=6.6 Hz), 4.91 (1H, t, J=6.4 Hz), 7.19—7.80 (13H, m), 8.08—8.13 (2H, m). FAB-MS m/z: 615 [M+H]⁺.

Methyl 4-[3-[4-(Chlorophenylsulfonyl)amino]-1-[3-[[E]-2-(7-chloro-2-quinolyl)vinyl]phenyl]propyl]thioacetate (6a). The title compound was prepared from methyl 4-mercaptobutylate in the same manner as described above, and obtained as a pale yellow solid. 1H-NMR (CDCl₃): 1.21—1.28 (3H, m), 1.71—1.85 (2H, m), 2.01—2.06 (2H, m), 2.26—2.39 (4H, m), 3.02—3.08 (2H, m), 3.84—3.88 (1H, m), 4.08—4.15 (2H, m), 4.79 (1H, t, J=6.4 Hz), 7.18—7.75 (11H, m), 8.08—8.13 (2H, m). FAB-MS m/z: 643 [M+H]⁺.

Methyl 4-[3-[4-(Chlorophenylsulfonyl)amino]-1-[3-[[E]-2-(7-chloro-2-quinolyl)vinyl]phenyl]propyl]thio-3,3-dimethylbutylate (6b). The title compound was prepared from methyl 3,3-dimethyl-4-mercaptobutylate in the same manner as described above, and obtained as a pale yel-
low solid. (94%). 1H-NMR (CDCl3): 0.96 (3H, s), 0.98 (3H, s), 2.03 (2H, q, J = 6.8 Hz), 2.23, 2.36 (each 1H, each d, J = 14.0 Hz), 2.38, 2.43 (each 1H, each d, J = 12.4 Hz), 3.07 (2H, m), 3.64 (3H, s), 3.81 (1H, t, J = 7.2 Hz), 4.90 (1H, t, J = 6.0 Hz), 7.17—7.87 (13H, m), 8.07—8.13 (2H, m). FAB-MS m/z: 657 [M+H]+.

(2) Benzyl 4-[[3-[4-Chlorophenylsulfonyl]amino]-1-[3-[(E)-2-(7-chloro-2-quinolyl)vinyl]phenyl]propyl]thio[methyl]-1-cyclopropanecarboxylate (6c) The title compound was prepared from benzyl 1-mercapto-n-propylcyclopropanecarboxylate in the same manner as described above, and obtained as a pale yellow solid. (93%). 1H-NMR (CDCl3): 0.96—2.02 (2H, m), 2.31—2.52 (4H, m), 2.93—3.10 (2H, m), 3.86 (1H, t, J = 13.6 Hz), 6.41—7.07 (13H, m), 7.76—8.11 (1H, m), 8.29 (1H, br d, J = 8.8 Hz). FAB-MS m/z: 731 [M+H]+.

(2) Methyl 4-[[3-[4-Chlorophenylsulfonyl]amino]-1-[3-[(E)-2-(7-chloro-2-quinolyl)vinyl]phenyl]propyl]thio[methyl]benzoate (6d) The title compound was prepared from methyl 4-mercapto-n-propylbenzoate in the same manner as described above, and obtained as a pale yellow solid. (93%). 1H-NMR (CDCl3): 1.97—2.03 (2H, m), 2.97 (2H, q, J = 6.8 Hz), 3.45 (1H, d, J = 13.6 Hz), 3.57 (1H, d, J = 13.6 Hz), 3.65 (1H, t, J = 8.0 Hz), 3.90 (3H, s), 4.38 (1H, d, J = 6.4 Hz), 7.12—8.14 (19H, m). FAB-MS m/z: 677 [M+H]+.

(2) Methyl 4-[[3-[4-Chlorophenylsulfonyl]amino]-1-[3-[(E)-2-(7-chloro-2-quinolyl)vinyl]phenyl]propyl]thio[methyl]phenylacetate (6e) The title compound was prepared from methyl 4-mercapto-n-phenylacetate in the same manner as described above, and obtained as a pale yellow solid. (quant.). 1H-NMR (CDCl3): 0.31—0.62 (4H, m), 5.80—6.07 (4H, m), 7.20—8.04 (20H, m). FAB-MS m/z: 597 [M+H]+.


(2) 1,3-benzyl 4-[[3-[(E)-2-(7-Chloro-2-quinolyl)vinyl]phenyl]ethylidene]methanesulfonate (15) An ice-cold mixture of potassium carbonate (25.3 g, 198 mmol), sodium borohydride (5.54 g, 147 mmol) and ethanol (580 ml) was added to the reaction mixture at 5 °C, and the mixture was stirred for 5 min. at room temperature. Diethyl ether was added to the residue and the resulting precipitate was collected by filtration to give 8.42 (1H, d, J = 8.8 Hz). FAB-MS m/z: 155 [M+H]+.

(2)-Methyl 4-[[3-[(E)-2-(7-Chloro-2-quinolyl)vinyl]phenyl]propyl]thio[methyl]benzoate (6h) The title compound was prepared from methyl 4-(2-mercaptoethyl)benzoate in the same manner as described above, and obtained as a colorless solid. 1H-NMR (CDCl3): 3.19 (3H, s), 3.95 (1H, d, J = 14.8 Hz), 4.27 (1H, dd, J = 14.8, 8.8 Hz), 4.99 (1H, d, J = 8.8 Hz), 7.70 (1H, br s), 7.89 (1H, d, J = 16.4 Hz), 7.93 (1H, d, J = 8.8 Hz), 7.99—8.03 (2H, m), 8.40 (1H, d, J = 8.8 Hz). FAB-MS m/z: 455 [M+H]+.

(2) 1,3-benzyl 4-[[3-[(E)-2-(7-Chloro-2-quinolyl)vinyl]phenyl]ethylidene]methanesulfonate (15) An ice-cold mixture of 14 (18.8 g, 39.1 mmol), pyridine (53 ml) and 1,2-dichloroethane was combined with methanesulfonic chloride (3.36 mol, 470 mmol), and the mixture was stirred at room temperature for 12 h. The reaction mixture was cooled to 10 °C, and acetic acid, an aqueous solution of potassium carbonate and brine, dried over MgSO4, and evaporated in vacuo. The residue was combined with acetonitrile, and the resulting precipitate was collected by filtration to give 15 (19.0 g) as a colorless solid. 1H-NMR (CDCl3—d2): 0.43—0.51 (4H, m), 2.30—2.45 (2H, m), 2.56—
The title compound was prepared from 16d and benzenesulfonyl chloride in the same manner as described above, and obtained as a pale yellow amorphous solid. (69%) H-NMR (CDCl₃): δ: 3.30—3.49 (2H, m), 3.50—3.75 (3H, m), 3.91 (3H, s), 4.66 (1H, t, J = 6.6 Hz), 6.91—7.95 (18H, m), 8.08—8.15 (2H, m). FAB-MS m/z: 672 [M⁺—H].

(±)-Methyl 4-[2-[2-(7-Chloro-2-quinolyl)vinyl][phenyl]methyl]benzoate (17b) The title compound was prepared from 16d and 4-bromobenzene sulfonyl chloride in the same manner as described above, and obtained as a pale yellow amorphous solid. (70%) H-NMR (CDCl₃): δ: 3.34—3.45 (2H, m), 3.54—3.75 (3H, m), 3.92 (3H, s), 4.90 (1H, t, J = 6.4 Hz), 7.06—8.32 (19H, m). FAB-MS m/z: 672 [M⁺—H].

(±)-4-[2-(2-Chloro-4-fluorophenyl)sulfonyl]amino]-1-[3-(2-chloro-2-quinolyl)vinyl][phenyl]ethyl][methyl]benzoate (17a) The title compound was prepared from 16c in the same manner as described above, and obtained as a pale yellow amorphous solid. (70%) H-NMR (CDCl₃): δ: 3.03—3.65 (2H, m), 3.85—4.00 (2H, m), 3.91 (3H, s), 4.30—4.40 (1H, m), 4.40—4.50 (1H, m), 7.15—7.75 (18H, m), 8.08—8.15 (2H, m). FAB-MS m/z: 663 [M⁺—H].

(±)-Methyl 3-[2-(2-Chloro-4-fluorophenyl)sulfonyl]amino]-1-[3-(2-chloro-2-quinolyl)vinyl]ethyl[phenyl]methyl]propionate (17a) The title compound was prepared from 16a in the same manner as described above, and obtained as a pale yellow amorphous solid. (49%) H-NMR (CDCl₃): δ: 2.40—2.71 (4H, m), 3.36—3.39 (2H, m), 3.66 (1H, s), 3.96 (1H, t, J = 7.4 Hz), 7.12—7.82 (13H, m), 8.09—8.15 (2H, m). FAB-MS m/z: 601 [M⁺—H].

(±)-Methyl 4-[2-(2-Chloro-4-fluorophenyl)sulfonyl]amino]-1-[3-(2-chloro-2-quinolyl)vinyl]ethyl[phenyl]3,3-dimethylbutylate (17b) The title compound was prepared from 16d in the same manner as described above, and obtained as a pale yellow amorphous solid. (55%) H-NMR (CDCl₃): δ: 0.42—0.55 (4H, m), 2.04—2.22 (2H, m), 2.48—2.52 (2H, m), 3.33 (2H, t, J = 6.4 Hz), 3.49 (1H, t, J = 7.2 Hz), 5.12 (2H, s), 7.13—7.78 (18H, m), 8.11—8.40 (2H, m). FAB-MS m/z: 717 [M⁺—H].

(±)-Methyl 4-[2-(2-Chloro-4-fluorophenyl)sulfonyl]amino]-1-[3-(E)-2-(7-chloro-2-quinolyl)vinyl][phenyl]ethyl][methyl]cyclopropylacetate (17c) The title compound was prepared from 16b in the same manner as described above, and obtained as a pale yellow amorphous solid. (44%) mp 76—78 °C. H-NMR (CDMSO-d₆): δ: 1.83—1.92 (2H, m), 2.10—2.12 (2H, m), 2.35—2.56 (4H, m), 3.01—3.18 (2H, m), 3.88 (1H, t, J = 7.2 Hz), 5.05 (1H, t, J = 6.4 Hz), 7.18—7.79 (13H, m), 8.05—8.15 (2H, m). FAB-MS m/z: 615 [M⁺—H].

(±)-Methyl 4-[2-(2-Chloro-4-fluorophenyl)sulfonyl]amino]-1-[3-(E)-2-(7-chloro-2-quinolyl)vinyl][phenyl]propyl][propiol]butyric Acid (7c) The title compound was prepared from 16b in the same manner as described above, and obtained as a pale yellow solid. (44%) mp 76—78 °C. H-NMR (CDMSO-d₆): δ: 1.83—1.92 (2H, m), 2.10—2.12 (2H, m), 2.35—2.56 (4H, m), 3.01—3.18 (2H, m), 3.88 (1H, t, J = 7.2 Hz), 5.05 (1H, t, J = 6.4 Hz), 7.18—7.79 (13H, m), 8.05—8.15 (2H, m). FAB-MS m/z: 615 [M⁺—H].

(±)-Methyl 4-[2-(4-Chlorophenyl)sulfonyl]amino]-1-[3-(E)-2-(7-chloro-2-quinolyl)vinyl][phenyl]ethyl][meth]ylen]cyclopropanecarboxylic Acid (7a) The title compound was prepared from 16a in the same manner as described above, and obtained as a pale yellow amorphous solid. (55%) H-NMR (CDCl₃): δ: 0.42—0.55 (4H, m), 2.04—2.22 (2H, m), 2.48—2.52 (2H, m), 3.33 (2H, t, J = 6.4 Hz), 3.49 (1H, t, J = 7.2 Hz), 5.12 (2H, s), 7.13—7.78 (18H, m), 8.11—8.40 (2H, m). FAB-MS m/z: 717 [M⁺—H].

(±)-Methyl 4-[2-(4-Chlorophenyl)sulfonyl]amino]-1-[3-(E)-2-(7-chloro-2-quinolyl)vinyl][phenyl]ethyl][methyl]cyclopropanecarboxylic Acid (17a) The title compound was prepared from 16e in the same manner as described above, and obtained as a pale yellow amorphous solid. (55%) H-NMR (CDCl₃): δ: 0.42—0.55 (4H, m), 2.04—2.22 (2H, m), 2.48—2.52 (2H, m), 3.33 (2H, t, J = 6.4 Hz), 3.49 (1H, t, J = 7.2 Hz), 5.12 (2H, s), 7.13—7.78 (18H, m), 8.11—8.40 (2H, m). FAB-MS m/z: 717 [M⁺—H].

(±)-Methyl 4-[2-(4-Chlorophenyl)sulfonyl]amino]-1-[3-(E)-2-(7-chloro-2-quinolyl)vinyl][phenyl]ethyl][methyl]benzoate (17b) The title compound was prepared from 16b in the same manner as described above, and obtained as a pale yellow amorphous solid. (79%) H-NMR (CDCl₃): δ: 2.64—2.68 (2H, m), 2.80—2.84 (2H, m), 3.34 (2H, t, J = 6.4 Hz), 3.87 (3H, s), 3.87—3.93 (1H, m), 7.14—7.95 (17H, m), 8.08—8.14 (2H, m). FAB-MS m/z: 677 [M⁺—H].

(±)-Methyl 4-[2-(4-Chlorophenyl)sulfonyl]amino]-1-[3-(E)-2-(7-chloro-2-quinolyl)vinyl][phenyl]ethyl][methyl]benzoate (17c) The title compound was prepared from 16d and benzenesulfonyl chloride in the same manner as described above, and obtained as a pale yellow amorphous solid. (69%) H-NMR (CDCl₃): δ: 3.30—3.49 (2H, m), 3.50—3.75 (3H, m), 3.91 (3H, s), 4.66 (1H, t, J = 6.6 Hz), 6.91—7.95 (18H, m), 8.08—8.15 (2H, m). FAB-MS m/z: 672 [M⁺—H].
The title compound was prepared from 6f in the same manner as described above, and obtained as a pale yellow amorphous solid. (70%). 1H-NMR (DMSO-d$_6$): δ: 1.95—2.09 (2H, m), 2.51—2.65 (2H, m), 2.75—2.87 (2H, m), 2.92—3.05 (2H, m), 3.84 (1H, t, J = 6.4 Hz), 4.93 (1H, m), 6.14—7.20 (13H, m), 7.34 (1H, t, J = 7.6 Hz), 7.42—7.51 (6H, m), 7.62—7.76 (5H, m), 7.90—7.99 (2H, m), 8.10—8.13 (2H, m), 13.6 Hz), 3.86 (1H, t, J = 4.7 Hz), 4.70—4.72 (1H, m), 7.13—7.20 (13H, m), 7.38 (1H, q, J = 6.8 Hz), 7.13—8.04 (14H, m), 8.28—8.43 (5H, m). FAB-MS m/z: 615 [M+H]$^+$. Anal. Calcd for C$_{34}$H$_{28}$N$_2$O$_4$S$_2$Cl$_2$: C, 61.54; H, 4.25; N, 4.45; S, 9.65; Cl, 5.11. Found: C, 57.13; H, 4.38; N, 4.16; S, 9.14; Br, 11.45; Cl, 5.10.

(2.4.4.4.4)-[1-[4-Chlorophenylsulfonylamino]-1-[3-(7-chloro-2-quinolyl)vinyl]phenyl]ethyl)ethyl]benzoic Acid (18e) The title compound was prepared from 17e in the same manner as described above, and obtained as a pale yellow solid. (74%). mp 192—193 °C. 1H-NMR (DMSO-d$_6$): δ: 3.21—3.29 (2H, m), 3.68 (1H, d, J = 13.6 Hz), 3.80 (1H, d, J = 13.6 Hz), 3.87 (1H, t, J = 7.6 Hz), 7.12—8.05 (13H, m), 8.42 (1H, d, J = 8.4 Hz), 8.12 (1H, brs). FAB-MS m/z: 633 [M+H]$^+$. Anal. Calcd for C$_{31}$H$_{28}$N$_3$O$_6$S$_2$Cl: C, 61.04; H, 4.14; N, 4.42; S, 9.13; Cl, 10.13. Found: C, 62.52; H, 4.05; N, 4.36; S, 10.12; Cl, 5.63; F, 3.06.

Biological Methods. Agonist-Induced Contraction of the Guinea Pig Ileum Guinea pigs weighing 370 to 740 g were sacrificed by exsanguination. The terminal ileum was removed and suspended in Tyrode's solution, which had the following composition: 136.8 mm NaCl, 2.7 mm KCl, 1.8 mm CaCl$_2$, 1.1 mm MgCl$_2$, 0.42 mm NaH$_2$PO$_4$, 11.9 mm NaHCO$_3$ and 5.6 mm glucose (pH 7.4). The ileum was divided into segments of approximately 40 mm in length and set in a Magnus vessel containing 10 ml of Tyrode's solution aerated with a 95% O$_2$–5% CO$_2$ mixture. The tissue was placed under tension using a 1-g load. The force generated by the tissue was isometrically measured. The ileum contractile response against 1 × 10$^{-5}$ m LTD$_4$ was first measured in the absence of the test compound and then in the presence of the compound at various concentrations. An IC$_{50}$ value was calculated by linear regression analysis (maximum–likelihood method) using SAS.

U46619-Induced Platelet Aggregation Using a syringe containing 1 volume of 3.8% sodium citrate aqueous solution, 9 volumes of blood were collected. Guinea pig and human PRP was obtained by centrifuging the blood for 10 min at 270 g. The remaining blood was further centrifuged at 110 × g for 10 min to yield PPP. The PRP was diluted with PPP to adjust the platelet counts to 500000 cells/μl. Platelet aggregation was induced by a stable analog of TxA$_2$, 1 × 10$^{-6}$ m U46619, and was measured using a NBS Hema Tracer VI (Nihok Bioscience, Tokyo, Japan). Various concentrations of the compounds were added to the PRP 2 min before the addition of U46619, and an IC$_{50}$ value (50% inhibition concentration) was

1. Platelet aggregation was induced by 10$^{-5}$ m U46619 in the absence of test compound and then in the presence of each test compound at various concentrations. Changes in the concentration of ADP were calculated by linear regression analysis (maximum–likelihood method) using SAS.
calculated from the inhibition ratio on the basis of the maximum light transmittance. All experiments were carried out within 4 h after blood collection to avoid a decrease in platelet sensitivity to U46619.

**LTD₄-Induced Acceleration of Plasma Leakage in Guinea Pig Skin**

Male Hartley guinea pigs whose back fur had been shaved with an electric clipper on the day before the experiment were given an intravenous administration of saline (1 ml per animal) containing 1% Evans blue. Two minutes later, 5 ng LTD₄ and the vehicle solution were administered intracutaneously on the back of the guinea pig (at 2 points for LTD₄ and 2 points for vehicle). The guinea pig was sacrificed by decapitation 30 min later. The skin was removed, and the visible blood in the isolated skin was also removed as much as possible. The pigment retained within the skin was then extracted by the addition of extraction buffer ([7 : 3] acetone : 0.5% Na₂SO₄ solution) and the amount of LTD₄-induced pigment leakage was measured using the 620 nm absorbance of the extract (UV-visible spectrophotometer, model UV-160A; Shimadzu, Kyoto). LTD₄-induced dye leakage was defined by subtracting the dye content in the vehicle-injected site from that in the LTD₄-induced site, so these calculated dye contents were collected for Evans blue dye remaining within the vasculature. This dye amount was used as an index of plasma leakage, although there was a potential uncontrolled hydrostatic pressure effect in this system. Test compounds were orally administered 1 h before intracutaneous administration of LTD₄.

**U46619-Induced Increase in Airway Resistance Increase**

Male Hartley guinea pigs were anesthetized by intraperitoneal injection of 1.2 g/kg, airway resistance was measured using a respiratory function measuring apparatus (Model 6; Busco Electronics, Inc., Sharon, CT, U.S.A.). The airway resistance was measured as the mean of every 5 s and expressed as the percentage change compared with the basal resistance level. The test compound was orally administered 1 h before intravenous administration of agonists. The effects of each compound were evaluated using the peak percentage change in lung resistance.

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**References and Notes**

1) Deceased July 22, 1996.