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 18 d 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)]: 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 chlorobenzenesulfonamide 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 chlorobenzenesulfonamide 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**[25)] was oxidized by manganese dioxide to afford the α,β-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 thionylchloride 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**[26)] 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

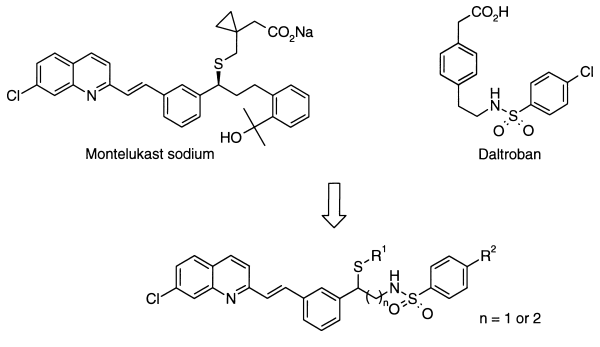

Fig. 1

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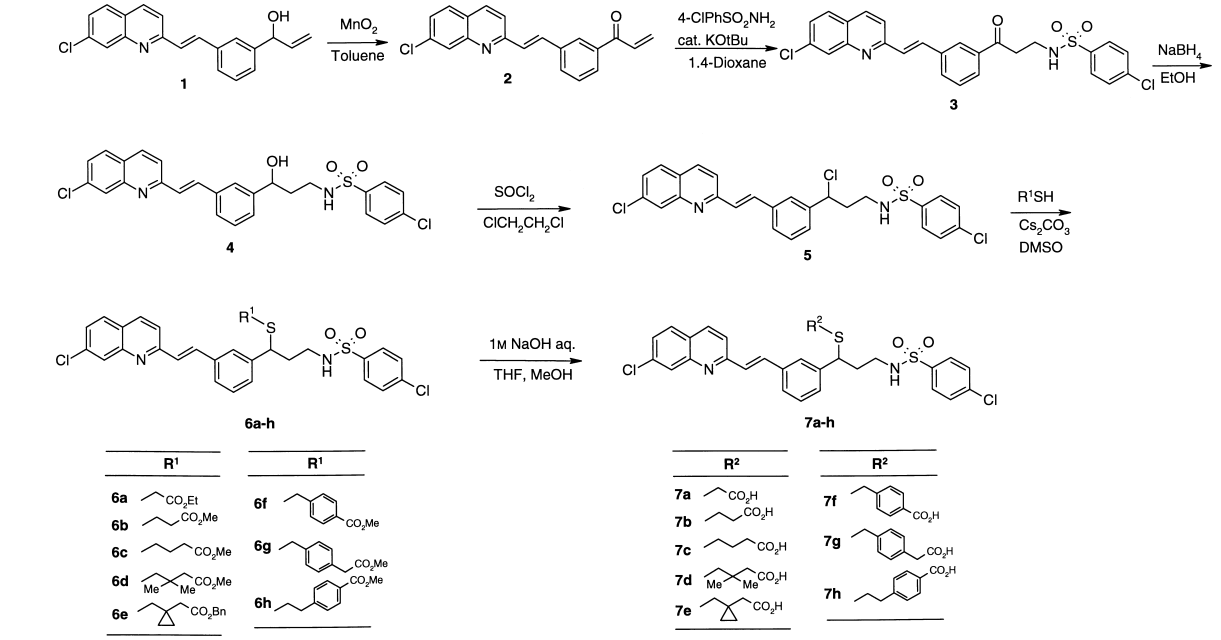


Chart 1

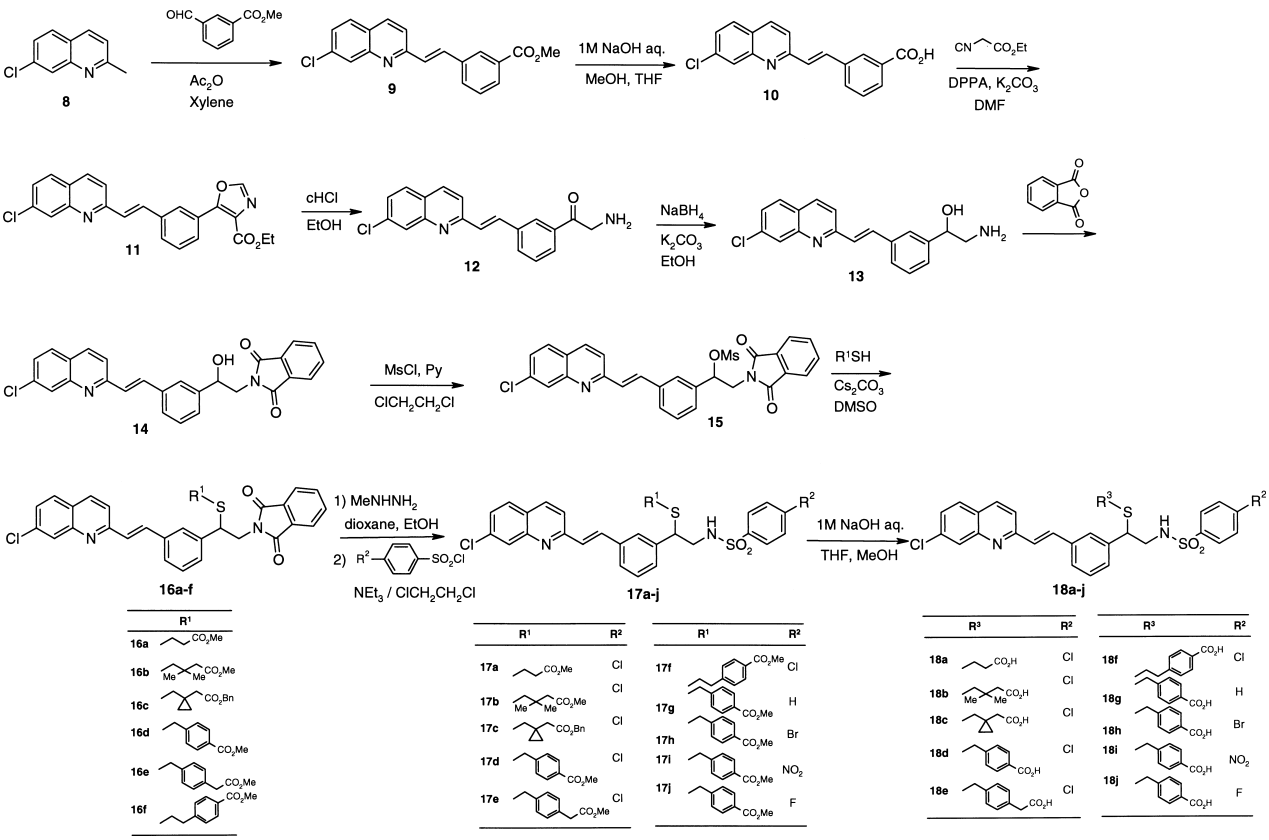


Chart 2

to afford the aminoalcohol **13**. The amino group of compound **13** was protected with phthalic anhydride, and the resulting phthalimide derivative was treated with methanesulfonyl 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 resulting 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 LTD_4-induced contraction in guinea pig ileum

were evaluated, and the results are listed in Table 1.

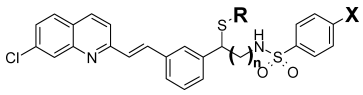
Among the 4-chlorobenzenesulfonamide propyl derivatives, the compound possessing an acetic acid group on the sulfur atom (**7a**) showed no TXA_2 antagonist activity. Replacement of the acetic acid group (**7a**) with propanoic acid group (**7b**) or butanoic acid group (**7c**) enhanced the TXA_2 antagonistic activity, and derivative **7c** showed particularly potent TXA_2 antagonist activity with an IC_{50} value of 150 nM. The introduction of 3,3-dimethyl (**7d**) or dimethylene (**7e**) groups on the butanoic acid reduced the TXA_2 antagonist activity, with IC_{50} 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 TXA_2 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 TXA_2 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 TXA_2 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 TXA_2 antagonistic activities with IC_{50} values of 340 nM and 510 nM, respectively. The compound with a 4-carbonylmethylphenylmethyl group (**18e**) on the sulfur atom showed reduced TXA_2 antagonistic activity, compared with compound **18d**. In the 4-chlorobenzenesulfonamide ethyl derivatives, introduction of a phenyl ring on the sulfur atom was favorable for TXA_2 antagonist activity.

Next, we investigated the influence of the substituent on the 4-position of the benzene sulfonamide group on TXA_2 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 TXA_2 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 TXA_2 antagonistic activity.

As shown in Table 1, montelukast has potent LTD_4 antagonistic activity with an IC_{50} value of 0.085 nM. In the series of 4-chlorobenzenesulfonamide propyl derivatives, the influence of the length of the methylene chain on the sulfur atom (**7a**—**c**) on the LTD_4 antagonistic activity differed from that for TXA_2 antagonistic activity. The compound with a propanoic acid group on the sulfur atom (**7b**) showed potent LTD_4 antagonist activity, with an IC_{50} 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 LTD_4 antagonistic activity. Compounds with dimethyl (**7d**) or dimethylene (**7e**) groups at the 3 position of the butanoic acid group in compound **7c** retained potent LTD_4 antagonist activities, with IC_{50} 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 LTD_4 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 LTD_4 antagonist activity suggesting that a phenyl group in this position causes a loss of this activity.

Table 1. TXA_2 and LTD_4 Antagonist Activities of Chloroquinolylvinyl Derivatives



No.	R	*n*	X	IC_{50} (nM)	
				TXA_2	LTD_4
7a	CO_2H	2	Cl	51000	1.2
7b	CO_2H	2	Cl	1000	0.41
7c	CO_2H	2	Cl	150	0.85
7d	Me Me CO_2H	2	Cl	1100	0.41
7e	CO_2H	2	Cl	500	0.21
7f	CO_2H	2	Cl	980	3.5
7g	CO_2H	2	Cl	4400	11
7h	CO_2H	2	Cl	1000	8.4
18a	CO_2H	1	Cl	9100	1.7
18b	Me Me CO_2H	1	Cl	10000	0.24
18c	CO_2H	1	Cl	1400	0.23
18d	CO_2H	1	Cl	340	0.40
18e	CO_2H	1	Cl	1100	2.1
18f	CO_2H	1	Cl	510	3.0
18g	CO_2H	1	H	680	0.041
18h	CO_2H	1	Br	500	0.077
18i	CO_2H	1	NO_2	1000	0.23
18j	CO_2H	1	F	750	0.12
	Daltroban			370	N.D.[a]
	Montelukast			N.D.[a]	0.085

a) Not determined.

Among the 4-chlorobenzenesulfonamide ethyl derivatives, the compound with a 2-propanoic acid group (**18a**) on the sulfur atom showed LTD_4 antagonist activity, with an IC_{50} value of 1.7 nM. Replacement of the carboxyethyl group in compound **18a** with 3,3-dimethylbuanoic acid (**18b**) or 3,3-dimethylenebutanoic acid (**18c**) groups on the sulfur atom increased the LTD_4 antagonist activity, with IC_{50} 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 LTD_4 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 IC_{50} value of 0.40 nM. The compounds with carboxymethylphenylmethyl (**18e**) or carboxyphenylethyl

Table 2. Inhibitory Activities of U46619-Induced Increase in Airway Resistance in Guinea Pig and LTD_4-Induced Acceleration of Plasma Leakage in Guinea Pig Skin

No.	U46619-induced airway resistance	LTD_4-induced plasma leakage
	ED_{50} (mg/kg) *p.o.*	ED_{50} (mg/kg) *p.o.*
7c	N.D.[a]	54%[c]
7e	38%[b]	0.12
18d	3.3	0.47
18g	N.D.[a]	63%[c]
18h	N.D.[a]	24%[c]
18j	N.D.[a]	44%[c]

a) Not determined. *b*) % inhibition at 10 mg/kg. *c*) % inhibition at 1 mg/kg.

(**18f**) groups showed less potent LTD_4 antagonist activity compared to compound **18d**, with IC_{50} 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 LTD_4 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 LTD_4 antagonistic activity, with IC_{50} values of 0.041 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**, **7e**, **18d**, **18g**, **18h**, **18j**) which possessed potent TXA_2 and LTD_4 antagonist activities were tested for their ability to inhibit the LTD_4-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 **7e** and **18d** showed potent inhibition of LTD_4-induced acceleration of plasma leakage, with ED_{50} 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 ED_{50} value of 3.3 mg/kg. Compound **7e** was less potent than compound **18d** in this respect.

In conclusion, in order to find an orally active TXA_2 and LTD_4 dual antagonist, we designed and synthesized chloroquinolylvinylphenyl derivatives based on the molecular structures of the TXA_2 antagonist daltroban and the LTD_4 antagonist montelukast. Among these compounds, **18d** showed potent TXA_2 and LTD_4 antagonist activity both *in vitro* and *in vivo*.

Experimental

^{1}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 ^{1}H-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 F_{254}.

1-{3-[(*E*)-2-(7-Chloro-2-quinolyl)vinyl]phenyl}propenone (2) A mixture of 1-{3-[(*E*)-2-(7-chloro-2-quinolyl)vinyl]phenyl}propenol (26.2 g, 81.4 mmol), manganese dioxide (131 g, 1.51 mol) and toluene (500 ml) was refluxed for 3 h. The reaction mixture was cooled to room temperature and then filtered through celite. The filtrate was evaporated *in vacuo*. Column chromatography of the residue on silica gel (AcOEt : $CHCl_3$: *n*-hexane = 3 : 30 : 70) gave **2** (10.6 g, 41%) as a colorless solid. ^{1}H-NMR ($CDCl_3$): 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* = 7.6 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-{3-[(*E*)-2-(7-chloro-2-quinolyl)vinyl]phenyl}-3-oxopropyl)benzenesulfonamide (3) A mixture of **2** (8.70 g, 27.2 mmol), 4-chlorobenzenesulfonamide (5.73 g, 29.9 mmol), potassium *tert*-butoxide (0.10 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 evaporated *in vacuo*. Column chromatography of the residue on silica gel (0.2% MeOH–$CHCl_3$) gave **3** (8.10 g, 58%) as a colorless solid. ^{1}H-NMR (DMSO-d_6): 3.15—3.21 (2H, m), 3.29 (2H, br t, *J* = 6.2 Hz), 7.57—7.63 (3H, m), 7.69 (2H, br d, *J* = 8.8 Hz), 7.83—7.89 (4H, m), 7.95 (1H, br s), 7.98 (1H, d, *J* = 6.4 Hz), 8.01—8.04 (3H, m), 8.23 (1H, br s), 8.44 (1H, d, *J* = 8.8 Hz). FAB-MS *m/z*: 511 $[M+H]^+$.

(±)-4-Chloro-*N*-(3-{3-[(*E*)-2-(7-chloro-2-quinolyl)vinyl]phenyl}-3-hydroxypropyl)benzenesulfonamide (4) A mixture of **3** (8.40 g, 17.7 mmol), tetrahydrofuran (40 ml) and ethanol (40 ml) was added to sodium borohydride (0.33 g, 8.8 mmol) at 5 °C. The reaction mixture was stirred at room temperature for 1 h, and then acidified with a 10% aqueous solution of citric acid. The mixture was extracted with $CHCl_3$, washed with brine, dried over Na_2SO_4, and evaporated *in vacuo* to give **4** (8.50 g, 90%) as a yellow amorphous solid. ^{1}H-NMR ($CDCl_3$): 1.88—1.93 (2H, m), 3.07—3.25 (2H, m), 4.86 (1H, br t, *J* = 6.2 Hz), 5.65 (1H, br t, *J* = 5.8 Hz), 7.16 (1H, br d, *J* = 8.0 Hz), 7.26—7.31 (2H, m), 7.44 (1H, dd, *J* = 8.8, 1.8 Hz), 7.46 (d, *J* = 8.4 Hz), 7.52 (1H, br s), 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, br d, *J* = 1.6 Hz), 8.07 (1H, d, *J* = 8.8 Hz). FAB-MS *m/z*: 513 $[M+H]^+$.

(±)-4-Chloro-*N*-(3-chloro-3-{3-[(*E*)-2-(7-chloro-2-quinolyl)vinyl]-phenyl}propyl)benzenesulfonamide (5) A solution of **4** (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 $CHCl_3$, washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. Column chromatography of the residue on silica gel (AcOEt : *n*-hexane = 1 : 4→3 : 7) gave **5** (8.52 g, quant.) as a yellow amorphous solid. ^{1}H-NMR ($CDCl_3$): 2.24—2.31 (2H, m), 3.10—3.25 (2H, m), 4.98 (1H, dd, *J* = 8.4, 6.0 Hz), 5.03 (1H, br t, *J* = 6.0 Hz), 7.26 (1H, d, *J* = 8.0 Hz), 7.34—7.39 (2H, m), 7.44 (1H, dd, *J* = 8.8, 2.0 Hz), 7.49 (2H, br d, *J* = 8.8 Hz), 7.56 (1H, d, *J* = 8.0 Hz), 7.58—7.66 (2H, m), 7.71 (2H, d, *J* = 8.8 Hz), 7.81 (2H, br d, *J* = 8.4 Hz), 8.05 (1H, br d, *J* = 2.0 Hz), 8.10 (1H, d, *J* = 8.4 Hz). FAB-MS *m/z*: 531 $[M+H]^+$.

(±) Methyl 4-[(3-{4-Chlorophenylsulfonylamino}-1-{3-[(*E*)-2-(7-chloro-2-quinolyl)vinyl]phenyl}propyl)thio]propionate (6b) A solution of **5** (0.50 g, 0.9 mmol) in *N*,*N*′-dimethylimidazolinone 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 $MgSO_4$, and evaporated *in vacuo*. Column chromatography of the residue on silica gel (AcOEt : *n*-hexane = 1 : 3) gave **6b** (0.32 g) as a yellow amorphous solid. ^{1}H-NMR ($CDCl_3$): 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 $[M+H]^+$.

(±) Ethyl 4-[(3-{4-Chlorophenylsulfonylamino}-1-{3-[(*E*)-2-(7-chloro-2-quinolyl)vinyl]phenyl}propyl)thio]acetate (6a) The title compound was prepared from ethyl mercaptoacetate in the same manner as described above, and obtained as a pale yellow solid. (82%). ^{1}H-NMR ($CDCl_3$): 1.20—1.30 (3H, m), 2.03—2.08 (2H, m), 2.71—3.13 (4H, m), 4.03—4.19 (3H, m), 7.00—8.13 (15H, m). FAB-MS *m/z*: 615 $[M+H]^+$.

(±) Methyl 4-[(3-{4-Chlorophenylsulfonylamino}-1-{3-[(*E*)-2-(7-chloro-2-quinolyl)vinyl]phenyl}propyl)thio]butylate (6c) The title compound was prepared from methyl 4-mercaptobutylate in the same manner as described above, and obtained as a pale yellow solid. (44%). ^{1}H-NMR ($CDCl_3$): 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-Chlorophenylsulfonylamino}-1-{3-[(*E*)-2-(7-chloro-2-quinolyl)vinyl]phenyl}propyl)thio]-3,3-dimethylbutylate (6d) 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%). ^{1}H-NMR ($CDCl_3$): 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 $[M+H]^+$.

(±) Benzyl 4-{[(3-{4-Chlorophenylsulfonylamino}-1-{3-[(*E*)-2-(7-chloro-2-quinolyl)vinyl]phenyl}propyl)thio]methyl}-1-cyclopropanacetate (6e) The title compound was prepared from benzyl 1-mercaptomethylcyclopropanacetate in the same manner as described above, and obtained as a pale yellow solid. (quant.). ^{1}H-NMR ($CDCl_3$): 0.31—0.62 (4H, m), 1.92—2.02 (2H, m), 2.31—2.52 (4H, m), 2.99—3.10 (2H, m), 3.86 (1H, t, J=7.6 Hz), 4.99 (1H, t, J=6.4 Hz), 5.11 (2H, s), 7.11—8.12 (20H, m). FAB-MS m/z: 731 $[M+H]^+$.

(±) Methyl 4-{[(3-{4-Chlorophenylsulfonylamino}-1-{3-[(*E*)-2-(7-chloro-2-quinolyl)vinyl]phenyl}propyl)thio]methyl}benzoate (6f) The title compound was prepared from methyl 4-mercaptomethylbenzoate in the same manner as described above, and obtained as a pale yellow solid. (93%). ^{1}H-NMR ($CDCl_3$): 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, t, J=6.4 Hz), 7.12—8.14 (19H, m). FAB-MS m/z: 677 $[M+H]^+$.

(±) Methyl 4-{[(3-{4-Chlorophenylsulfonylamino}-1-{3-[(*E*)-2-(7-chloro-2-quinolyl)vinyl]phenyl}propyl)thio]methyl}phenylacetate (6g) The title compound was prepared from methyl 4-mercaptometylphenylacetate in the same manner as described above, and obtained as a pale yellow solid. (39%). ^{1}H-NMR ($CDCl_3$): 2.00—2.06 (2H, m), 2.95—3.00 (2H, m), 3.27—3.72 (4H, m), 3.68 (3H, s), 4.76—4.80 (1H, m), 7.04—7.89 (17H, m), 8.25—8.40 (2H, m). FAB-MS m/z: 691 $[M+H]^+$.

(±) Methyl 4-{2-[(3-{4-Chlorophenylsulfonylamino}-1-{3-[(*E*)-2-(7-chloro-2-quinolyl)vinyl]phenyl}propyl)thio]ethyl}benzoate (6h) The title compound was prepared from methyl 4-(2-mercaptoethyl)benzoate in the same manner as described above, and obtained as a pale yellow amorphous solid. (49%). ^{1}H-NMR ($CDCl_3$) δ: 2.00—2.06 (2H, m), 2.50—2.60 (2H, m), 2.70—2.82 (2H, m), 2.95—3.02 (2H, m), 3.82 (1H, t, J=7.4 Hz), 3.87 (3H, s), 4.54 (1H, t, J=6.4 Hz), 7.20 (1H, d, J=7.6 Hz), 7.33—7.41 (2H, m), 7.44—7.50 (3H, m), 7.53 (1H, br s), 7.66 (2H, d, J=8.8 Hz), 7.72 (2H, d, J=8.8 Hz), 8.08 (1H, br d, J=1.6 Hz), 8.12 (1H, d, J=8.4 Hz). FAB-MS m/z: 691 $[M+H]^+$.

Methyl 3-[(*E*)-2-(7-Chloro-2-quinolyl)vinyl]benzoate (9) A mixture of 7-chloroquinaldine (**8**, 5.40 g, 30.4 mmol), methyl isophthalaldehyde (5.99 g, 36.5 mmol) and acetic anhydride (8.61 ml, 91.2 mmol) in xylene (54 ml) was stirred under reflux for 8 h. The reaction mixture was cooled to room temperature, and the solvent was evaporated under reduced pressure. Diethylether was added to the residue and the resulting precipitate was collected by filtration to give **9** (4.65 g) as a colorless solid. ^{1}H-NMR (DMSO-d_6) δ: 3.91 (3H, s), 7.50—7.65 (3H, m), 7.90—8.08 (6H, m), 8.27 (1H, br s), 8.42 (1H, d, J=8.8 Hz). FAB-MS m/z: 324 $[M+H]^+$.

3-[(*E*)-2-(7-Chloro-2-quinolyl)vinyl]benzoic Acid (10) A mixture of **9** (4.60 g, 14.2 mmol), tetrahydrofurane (46 ml) and methanol (23 ml) was combined with aqueous 1 M NaOH solution (21 ml) and stirred at 40 °C. for 3 h. The reaction mixture was acidified with an aqueous 10% citric acid solution and the resulting precipitate was collected by filtration to give **10** as a colorless solid. ^{1}H-NMR (DMSO-d_6) δ: 7.53—7.62 (3H, m), 7.93—8.04 (6H, m), 8.28 (1H, br s), 8.42 (1H, d, J=8.8 Hz), 12.6—13.8 (1H, br s). FAB-MS m/z: 308 $[M-H]^+$.

Ethyl 5-{3-[(*E*)-2-(7-Chloro-2-quinolyl)vinyl]phenyl}oxazol-4-carboxylate (11) A solution of **10** (4.70 g, 15.2 mmol) in dimethylformamide (70 ml) was combined with potassium carbonate, 1.5 hydrate (5.01 g, 30.3 mmol) and ethyl isocyanoacetate (2.23 g, 19.7 mmol), and then stirred for 5 min. at room temperature. Diphenylphosphoryl azide (5.01 g, 18.2 mmol) was added to the reaction mixture at 5 °C, and the mixture was stirred for 20 h at room temperature. Ice-water was added to the reaction mixture, which was then extracted with ethyl acetate. The organic layer was washed with water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. Column chromatography of the residue on silica gel (5% ethyl acetate–$CHCl_3$) gave **11** (5.01 g, 93%) as a colorless solid. ^{1}H-NMR (DMSO-d_6) δ: 1.29 (3H, t, J=7.2 Hz), 4.33 (2H, q, J=7.2 Hz), 7.54—7.65 (3H, m), 7.89—7.96 (4H, m), 8.01 (2H, d, J=8.8 Hz), 8.04 (1H, br d, J=2.0 Hz), 8.32 (1H, br s), 8.42 (1H, d, J=8.4 Hz), 8.63 (1H, s). EI-MS m/z: 404 $[M^+]$.

2-Amino-1-{3-[(*E*)-2-(7-chloro-2-quinolyl)vinyl]phenyl}ethanone Dihydrochloride (12) A mixture of **11** (5.00 g, 12.4 mmol), ethanol (25 ml) and concentrated HCl (25 ml) was stirred under reflux for 6 h. The reaction mixture was cooled to room temperature, and the resulting precipitate was collected by filtration to give **12** (4.80 g, 98%) as a colorless solid. ^{1}H-NMR (DMSO-d_6) δ: 2.52 (2H, br d, J=5.9 Hz), 7.72 (1H, t, J=7.6 Hz), 7.78 (1H, dd, J=8.8, 2.0 Hz), 7.87 (1H, d, J=16.6 Hz), 8.06—8.10 (2H, m), 8.19 (1H, d, J=8.8 Hz), 8.25 (1H, d, J=8.8 Hz), 8.30—8.38 (3H, m), 8.59 (3H, br s), 8.80 (1H, d, J=8.8 Hz). FAB-MS m/z: 323 $[M+H]^+$.

(±)-2-Amino-1-{3-[(*E*)-2-(7-chloro-2-quinolyl)vinyl]phenyl}ethanol (13) 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 **12** (38.7 g, 98 mmol) in portions with the temperature maintained below 15 °C. The reaction mixture was stirred at room temperature for 1 h and then poured into ice-water. The resulting precipitate was collected by filtration to give **13** (21.20 g, 55%) as a colorless solid. ^{1}H-NMR (DMSO-d_6) δ: 2.65 (1H, dd, J=13.0, 7.8 Hz), 2.74 (1H, t, J=13.0, 4.4 Hz), 4.51 (1H, br dd, J=7.2, 4.4 Hz) 7.33 (1H, d, J=8.0 Hz), 7.39 (1H, t, J=7.6 Hz), 7.47 (1H, d, J=16.4 Hz), 7.56—7.63 (2H, m), 7.70 (1H, br s), 7.88 (1H, d, J=16.4 Hz), 7.93 (1H, d, J=8.4 Hz), 7.99—8.03 (2H, m), 8.40 (1H, d, J=8.4 Hz). FAB-MS m/z: 325 $[M+H]^+$.

(±)-*N*-(2-{3-[(*E*)-2-(7-Chloro-2-quinolyl)vinyl]phenyl}-2-hydroxyethyl)phthalimide (14) A mixture of **13** (16.10 g, 49.6 mmol), phthalic anhydride (7.34 g, 49.6 mmol) and toluene (20 ml) was stirred and heated to 160 °C, and then stirred under reduced pressure (3 mmHg) for 3 h. The reaction mixture was cooled to room temperature, and then acetonitrile was added. The resulting precipitate was collected by filtration to give **14** (18.8 g) as a colorless solid. ^{1}H-NMR (DMSO-d_6) δ: 3.72 (1H, dd, J=13.2, 4.6 Hz), 3.83 (1H, dd, J=13.2, 8.8 Hz), 4.96—5.01 (1H, m), 5.74 (1H, d, J=4.4 Hz) 7.33—7.48 (3H, m), 7.59 (1H, dd, J=8.0, 2.0 Hz), 7.76 (1H, br d, J=7.6 Hz), 7.75 (1H, br s), 7.82—7.95 (6H, m), 8.00 (1H, d, J=8.0 Hz), 8.03 (1H, d, J=2.0 Hz), 8.40 (1H, d, J=8.8 Hz). FAB-MS m/z: 455 $[M+H]^+$.

(±)-1-{3-[(*E*)-2-(7-Chloro-2-quinolyl)vinyl]phenyl}-2-phthalimidoethylmethanesulfonate (15) An ice-cold mixture of **14** (17.8 g, 39.1 mmol), pyridine (53 ml) and 1,2-dichloroethane was combined with methanesulfonylchloride (3.36 ml, 47.0 mmol), and the mixture was stirred at room temperature for 12 h. The reaction mixture was acidified with 10% aqueous solution of citric acid, and then the mixture was extracted with $CHCl_3$. The organic layer was washed with a 10% aqueous solution of citric acid, a 5% aqueous solution of potassium carbonate and brine, dried over $MgSO_4$, 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. ^{1}H-NMR (DMSO-d_6) δ: 3.19 (3H, s), 3.95 (1H, dd, J=14.8, 4.0 Hz), 4.27 (1H, dd, J=14.8, 8.8 Hz), 5.89 (1H, dd, J=8.8, 4.0 Hz), 7.51—7.56 (2H, m), 7.59—7.63 (2H, m), 7.79—7.83 (1H, m), 7.84—7.89 (2H, m), 7.90—7.96 (5H, m), 8.00—8.04 (2H, m), 8.43 (1H, d, J=8.8 Hz). FAB-MS m/z: 533 $[M+H]^+$.

(±)-Methyl 4-{[(1-{3-[(*E*)-2-(7-Chloro-2-quinolyl)vinyl]phenyl}-2-phthalimidoethyl)thio]methyl}benzoate (16d) A mixture of **15** (3.00 g, 5.6 mmol), methyl 4-mercaptomethylbenzoate (1.54 g, 8.4 mmol) and dimethylsulfoxide (90 ml) was combined with cesium carbonate (3.96 g, 11.3 mmol) at 20 °C. The reaction mixture was stirred at room temperature for 1 h, and then benzene, ice and water were added. The reaction mixture was filtered, and the organic layer of the filtrate was washed with water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. Column chromatography of the residue on silica gel (benzene→5% AcOEt-benzene) gave **16d** (1.54 g) as a colorless solid. ^{1}H-NMR (DMSO-d_6) δ: 3.58 (1H, d, J=13.2 Hz), 3.70 (1H, d, J=13.2 Hz), 3.88 (3H, s), 4.00—4.16 (3H, m), 4.28 (1H, t, J=8.0 Hz), 7.24—7.93 (17H, m), 8.08—8.13 (2H, m). FAB-MS m/z: 619 $[M+H]^+$.

(±)-Methyl 3-[(1-{3-[(*E*)-2-(7-Chloro-2-quinolyl)vinyl]phenyl}-2-phthalimidoethyl)thio]propanoate (16a) The title compound was prepared from methyl 3,3-dimethyl-4-mercapto-butylate in the same manner as described above, and obtained as a pale yellow solid. (15%). ^{1}H-NMR ($CDCl_3$) δ: 2.40—2.43 (2H, m), 2.64—2.76 (2H, m), 3.61 (3H, s), 4.11—4.20 (2H, m), 4.46 (1H, t, J=8.0 Hz), 7.33—7.91 (13H, m), 8.07—8.12 (2H, m). FAB-MS m/z: 557 $[M+H]^+$.

(±)-Methyl 4-[(1-{3-[(*E*)-2-(7-Chloro-2-quinolyl)vinyl]phenyl}-2-phthalimidoethyl)thio]-3,3-dimethylbutylate (16b) The title compound was prepared from methyl 3,3-dimethyl-4-mercapto-butylate in the same manner as described above, and obtained as a pale yellow solid. (41%). ^{1}H-NMR ($CDCl_3$) δ: 0.99 (6H, s), 2.18—2.27 (2H, m), 2.51—2.60 (2H, m), 3.60 (3H, s), 4.10—4.13 (2H, m), 4.40 (1H, t, J=8.0 Hz), 7.31—7.83 (13H, m), 8.07—8.12 (2H, m). FAB-MS m/z: 599 $[M+H]^+$.

(±)-Benzyl {[(1-{3-[(*E*)-2-(7-Chloro-2-quinolyl)vinyl]phenyl}-2-phthalimidoethyl)thio]methyl}cyclopropanacetate (16c) The title compound was prepared from benzyl (1-mercaptomethyl)cyclopropanacetate in the same manner as described above, and obtained as a pale yellow solid. (46%). ^{1}H-NMR ($CDCl_3$) δ: 0.43—0.51 (4H, m), 2.30—2.45 (2H, m), 2.56—

2.60 (2H, m), 4.07—4.10 (2H, m), 4.43—4.47 (1H, m), 5.05 (2H, s), 7.27—7.81 (18H, m), 8.07—8.11 (2H, m). FAB-MS *m/z*: 673 $[M+H]^+$.

(±)-Methyl 4-{[(1-{3-[(*E*)-2-(7-Chloro-2-quinolyl)vinyl]phenyl}-2-phthalimidoethyl)thio]methyl}phenylacetate (16e) The title compound was prepared from methyl 3,3-dimethyl-4-mercapto-butylate in the same manner as described above, and obtained as a pale yellow solid. (34%). ^{1}H-NMR ($CDCl_3$) δ: 3.70 (1H, d, J=14.0 Hz), 3.82 (3H, s), 3.84 (1H, d, J=14.0 Hz), 3.98 (1H, dd, J=14.4, 8.0 Hz), 4.09 (1H, dd, J=14.4, 8.0 Hz), 4.24 (1H, t, J=8.0 Hz), 7.29—7.40 (4H, m), 7.45 (1H, d, J=16.8 Hz), 7.59—7.68 (3H, m), 7.77—7.86 (7H, m), 7.93 (1H, d, J=8.8 Hz), 8.00—8.04 (2H, m), 8.41 (1H, d, J=8.4 Hz). FAB-MS *m/z*: 619 $[M+H]^+$.

(±)-Methyl 4-{[(1-{3-[(*E*)-2-(7-Chloro-2-quinolyl)vinyl]phenyl}-2-phthalimidoethyl)thio]-2-ethyl}benzoate (16f) The title compound was prepared from methyl 4-(2-mercaptoethyl)benzoate in the same manner as described above, and obtained as a pale yellow solid. (26%). ^{1}H-NMR ($CDCl_3$) δ: 2.64—2.73 (2H, m), 2.80—2.84 (2H, m), 3.85 (3H, s), 4.10—4.15 (2H, m), 4.44 (1H, t, J=8.4 Hz), 7.11—7.94 (17H, m), 8.07—8.12 (2H, m). FAB-MS *m/z*: 633 $[M+H]^+$.

(±)-Methyl 4-{[(2-{4-Chlorophenylsulfonylamino}-1-{3-[(*E*)-2-(7-chloro-2-quinolyl)vinyl]phenyl}ethyl)thio]methyl}benzoate (17d) A mixture of **16d** (1.50 g, 2.4 mmol), 1,4-dioxane (10 ml) and ethanol (20 ml) was com-bined with methylhydrazine (1.55 ml, 29.0 mmol), and stirred under reflux for 7 h. The reaction mixture was cooled to room temperature, and then ice and a 5% aqueous solution of potassium carbonate were added. The reaction mixture was extracted with 1,2-dichloroethane, washed with a 5% aqueous solution of potassium carbonate and brine, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was dissolved in 1,2-dichloromethane, cooled to 5 °C and combined with triethylamine (0.51 ml, 3.6 mmol) and 4-chlorobenzenesulfonyl chloride (0.61 g, 2.9 mmol). The reaction mixture was stirred for 12 h at 5 °C, and then acidified with a 10% aqueous solution of citric acid. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. Column chromatography of the residue on silica gel (3% AcOEt–benzene→5% AcOEt–benzene) gave **17d** (1.03 g, 65%) as a colorless solid. ^{1}H-NMR (DMSO-d_6) δ: 3.30—3.45 (2H, m), 3.55 (1H, d, J=13.6 Hz), 3.67 (1H, d, J=13.6 Hz), 3.71 (1H, t, J=6.4 Hz), 3.91 (3H, s), 4.69 (1H, t, J=6.0 Hz), 7.06—7.75 (13H, m), 7.97 (2H, d, J=8.0 Hz), 8.08—8.15 (2H, m). FAB-MS *m/z*: 663 $[M+H]^+$.

(±)-Methyl 3-[(2-{4-Chlorophenylsulfonylamino}-1-{3-[(*E*)-2-(7-chloro-2-quinolyl)vinyl]phenyl}ethyl)thio]propanoate (17a) The title compound was prepared from **16a** in the same manner as described above, and obtained as a pale yellow amorphous solid. (49%). ^{1}H-NMR ($CDCl_3$) δ: 2.40—2.71 (4H, m), 3.36—3.39 (2H, m), 3.66 (3H, 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-{4-Chlorophenylsulfonylamino}-1-{3-[(*E*)-2-(7-chloro-2-quinolyl)vinyl]phenyl}ethyl)thio]-3,3-dimethylbutylate (17b) The title compound was prepared from **16b** in the same manner as described above, and obtained as a pale yellow amorphous solid. (60%). ^{1}H-NMR ($CDCl_3$) δ: 0.99 (6H, s), 2.22—2.34 (2H, m), 2.48 (1H, d, J=12.0 Hz), 2.55 (1H, d, J=12.0 Hz), 3.38 (2H, t, J=6.8 Hz), 3.75 (3H, s), 3.88 (1H, t, J=7.2 Hz), 4.91 (1H, m), 7.17—7.78 (13H, m), 8.08—8.14 (2H, m). FAB-MS *m/z*: 643 $[M+H]^+$.

(±)-Benzyl 1-{[(2-{4-Chlorophenylsulfonylamino}-1-{3-[(*E*)-2-(7-chloro-2-quinolyl)vinyl]phenyl}ethyl)thio]methyl}cyclopropylacetate (17c) The title compound was prepared from **16c** in the same manner as described above, and obtained as a pale yellow amorphous solid. (55%). ^{1}H-NMR ($CDCl_3$) δ: 0.42—0.55 (4H, m), 2.40—2.42 (2H, m), 2.48—2.56 (2H, m), 3.33 (2H, t, J=6.4 Hz), 3.93 (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-Chlorophenylsulfonylamino}-1-{3-[(*E*)-2-(7-chloro-2-quinolyl)vinyl]phenyl}ethyl)thio]methyl}phenylacetate (17e) The title compound was prepared from **16e** in the same manner as described above, and obtained as a pale yellow amorphous solid. (54%). ^{1}H-NMR (DMSO-d_6) δ: 3.23—3.35 (2H, m), 3.69 (1H, d, J=14.0 Hz), 3.81 (1H, d, J=14.0 Hz), 3.84 (3H, s), 3.85—3.89 (1H, m), 4.17 (1H, d, J=8.0 Hz), 7.35—7.39 (3H, m), 7.45 (1H, d, J=16.4 Hz), 7.49 (1H, br s), 7.57—7.64 (4H, m), 7.59—7.73 (2H, m), 7.82 (1H, d, J=16.4 Hz), 7.90 (2H, br d, J=8.0 Hz), 7.93 (1H, d, J=9.2 Hz), 8.00—8.04 (3H, m), 8.42 (1H, d, J=8.4 Hz). FAB-MS *m/z*: 619 $[M+H]^+$.

(±)-Methyl 4-{[(2-{4-Chlorophenylsulfonylamino}-1-{3-[(*E*)-2-(7-chloro-2-quinolyl)vinyl]phenyl}ethyl)thio]-2-ethyl}benzoate (17f) The title compound was prepared from **16f** in the same manner as described above, and obtained as a pale yellow amorphous solid. (79%). ^{1}H-NMR ($CDCl_3$) 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-{Phenylsulfonylamino}-1-{3-[(*E*)-2-(7-chloro-2-quinolyl)vinyl]phenyl}ethyl)thio]methyl}benzoate (17g) 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%). ^{1}H-NMR ($CDCl_3$) δ: 3.30—3.49 (2H, m), 3.50—3.75 (3H, m), 3.91 (3H, s), 4.66 (1H, t, J=6.4 Hz), 6.91—7.95 (18H, m), 8.08—8.15 (2H, m). FAB-MS *m/z*: 627 $[M-H]^+$.

(±)-Methyl 4-{[(2-{4-Bromophenylsulfonylamino}-1-{3-[(*E*)-2-(7-chloro-2-quinolyl)vinyl]phenyl}ethyl)thio]methyl}benzoate (17h) The title compound was prepared from **16d** and 4-bromobenzenesulfonyl chloride in the same manner as described above, and obtained as a pale yellow amorphous solid. (67%). ^{1}H-NMR ($CDCl_3$) δ: 3.25—3.40 (2H, m), 3.52—3.72 (3H, m), 3.91 (3H, s), 4.72 (1H, t, J=6.4 Hz), 7.03—7.75 (15H, m), 7.92—8.02 (4H, m). FAB-MS *m/z*: 706 $[M-H]^+$.

(±)-Methyl 4-{[(2-{4-Nitrophenylsulfonylamino}-1-{3-[(*E*)-2-(7-chloro-2-quinolyl)vinyl]phenyl}ethyl)thio]methyl}benzoate (17i) The title compound was prepared from **16d** and 4-nitrobenzenesulfonyl chloride in the same manner as described above, and obtained as a pale yellow amorphous solid. (68%). ^{1}H-NMR ($CDCl_3$) δ: 3.30—3.95 (2H, m), 3.54—3.75 (3H, m), 3.92 (3H, s), 4.96 (1H, t, J=6.4 Hz), 6.90—8.30 (19H, m). FAB-MS *m/z*: 672 $[M+H]^+$.

(±)-Methyl 4-{[(2-{4-Fluorophenylsulfonylamino}-1-{3-[(*E*)-2-(7-chloro-2-quinolyl)vinyl]phenyl}ethyl)thio]methyl}benzoate (17j) 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. (70%). ^{1}H-NMR ($CDCl_3$) 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-[(3-{4-Chlorophenylsulfonylamino}-1-{3-[(*E*)-2-(7-chloro-2-quinolyl)vinyl]phenyl}propyl)thio]propionic Acid (7b) A mixture of **6b** (0.30 g, 0.49 mmol), tetrahydrofuran (6 ml) and methanol (3 ml) was combined with a 1 M aqueous solution of NaOH (1.2 ml, 1.2 mmol). The reaction mixture was stirred at room temperature for 12 h, and then acidified with 10% aqueous solution of citric acid. The reaction mixture was extracted with chloroform, washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. Following column chromatography of the residue on silica gel (AcOEt : *n*-hexane=3 : 7) gave **7b** (0.08 g, 27%) as a pale yellow amorphous. ^{1}H-NMR (DMSO-d_6) δ: 1.89—2.00 (2H, m), 2.31—2.50 (2H, m), 2.71—2.76 (2H, m), 3.33—3.39 (2H, m), 3.82—4.01 (1H, m), 7.21—8.16 (14H, m), 8.42 (1H, d, J=8.8 Hz), 12.23 (1H, s). FAB-MS *m/z*: 601 $[M+H]^+$. *Anal.* Calcd for $C_{29}H_{26}N_2O_4S_2Cl_2$: C, 57.90; H, 4.36; N, 4.66; S, 10.66; Cl, 11.79. Found: C, 57.78; H, 4.45; N, 4.58; S, 10.50; Cl, 11.89.

(±)-4-[(3-{4-Chlorophenylsulfonylamino}-1-{3-[(*E*)-2-(7-chloro-2-quinolyl)vinyl]phenyl}propyl)thio]acetic Acid (7a) The title compound was prepared from **6a** in the same manner as described above, and obtained as a pale yellow amorphous solid. (33%). ^{1}H-NMR (DMSO-d_6) δ: 1.91—2.04 (2H, m), 2.70—2.78 (2H, m), 2.94 (1H, d, J=14.2 Hz), 3.10 (1H, d, J=14.2 Hz), 4.06 (1H, t, J=7.6 Hz), 6.86—8.16 (14H, m), 8.42 (1H, d, J=8.8 Hz). FAB-MS *m/z*: 587 $[M+H]^-$. *Anal.* Calcd for $C_{28}H_{24}N_2O_4S_2Cl_2$: C, 57.24; H, 4.12; N, 4.77; S, 10.92; Cl, 12.07. Found: C, 56.86; H, 4.12; N, 4.56; S, 11.06; Cl, 12.04.

(±)-4-[(3-{4-Chlorophenylsulfonylamino}-1-{3-[(*E*)-2-(7-chloro-2-quinolyl)vinyl]phenyl}propyl)thio]butylic Acid (7c) The title compound was prepared from **6c** in the same manner as described above, and obtained as a pale yellow solid. (44%). mp 76—78 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.83—1.92 (1H, 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 $[M+H]^+$. *Anal.* Calcd for $C_{30}H_{28}N_2O_4S_2Cl_2 \cdot 0.3C_2H_3N \cdot 0.3H_2O$: C, 58.03; H, 4.69; N, 5.09; S, 10.13; Cl, 11.20. Found: C, 57.98; H, 4.50; N, 5.04; S, 10.19; Cl, 11.33.

(±)-4-[(3-{4-Chlorophenylsulfonylamino}-1-{3-[(*E*)-2-(7-chloro-2-quinolyl)vinyl]phenyl}propyl)thio]-3,3-dimethylbutylic Acid (7d) The title compound was prepared from **6d** in the same manner as described above, and obtained as a pale yellow solid. (40%). mp 86—89 °C. ^{1}H-NMR (DMSO-d_6) δ: 0.93 (6H, s), 1.89—2.03 (2H, m), 2.09—2.17 (2H, m), 2.34 (1H, d, J=12.8 Hz), 2.43 (1H, d, J=12.8 Hz) 2.70—2.79 (2H, m), 3.88 (1H, t, J=8.4 Hz), 7.22—8.04 (14H, m), 8.42 (1H, d, J=8.4 Hz), 12.00 (1H, br s). FAB-MS *m/z*: 643 $[M+H]^+$. *Anal.* Calcd for $C_{32}H_{32}N_2O_4S_2Cl_2$: C, 59.71; H, 5.01; N, 4.35; S, 9.96; Cl, 11.02. Found: C, 59.80; H, 4.94; N, 4.38; S, 9.72; Cl, 11.30.

(±)-4-{[(3-{4-Chlorophenylsulfonylamino}-1-{3-[(*E*)-2-(7-chloro-2-quinolyl)vinyl]phenyl}propyl)thio]methyl}-1-cyclopropanacetic Acid (7e) The title compound was prepared from **6e** in the same manner as de-

scribed above, and obtained as a pale yellow solid. (40%). mp 97—100 °C. ^{1}H-NMR (DMSO-d_6) δ: 0.31—0.45 (4H, m), 1.88—1.99 (2H, m), 2.21—2.29 (2H, m), 2.43—2.51 (2H, m), 2.67—2.73 (2H, m), 3.93 (1H, t, J=8.4 Hz), 7.22—8.03 (14H, m), 8.42 (1H, d, J=8.4 Hz), 12.01 (1H, br s). FAB-MS m/z: 641 $[M+H]^+$. *Anal.* Calcd for $C_{32}H_{30}N_2O_4S_2Cl_2$: C, 59.90; H, 4.71; N, 4.37; S, 10.00; Cl, 11.05. Found: C, 59.69; H, 4.56; N, 4.31; S, 10.05; Cl, 11.00.

(±)-4-{[(3-{4-Chlorophenylsulfonylamino}-1-{3-[(*E*)-2-(7-chloro-2-quinolyl)vinyl]phenyl}propyl)thio]methyl}benzoic Acid (7f) The title compound was prepared from **6f** in the same manner as described above, and obtained as a pale yellow amorphous solid. (65%). ^{1}H-NMR (DMSO-d_6) δ: 1.93—2.01 (2H, m), 2.68—2.71 (2H, m), 3.56 (1H, d, J=13.2 Hz), 3.66 (1H, d, J=13.2 Hz), 3.87 (1H, t, J=7.2 Hz), 7.20—8.04 (18H, m), 8.42 (1H, d, J=8.8 Hz), 12.87 (1H, br s). FAB-MS m/z: 663 $[M+H]^+$. *Anal.* Calcd for $C_{34}H_{28}N_2O_4S_2Cl_2$: C, 61.54; H, 4.25; N, 4.22; S, 9.66; Cl, 10.68. Found: C, 61.29; H, 4.29; N, 4.14; S, 9.43; Cl, 10.38.

(±)-4-{[(3-{4-Chlorophenylsulfonylamino}-1-{3-[(*E*)-2-(7-chloro-2-quinolyl)vinyl]phenyl}propyl)thio]methyl}phenylacetic Acid (7g) The title compound was prepared from **6g** in the same manner as described above, and obtained as a pale yellow solid. (20%). mp 76—78 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.94—2.03 (2H, m), 2.65—2.75 (2H, m), 3.36—3.57 (4H, m), 3.74—3.91 (1H, m), 7.08—8.00 (18H, m), 8.42 (1H, d, J=8.0 Hz), 12.31 (1H, br s). FAB-MS m/z: 677 $[M+H]^+$. *Anal.* Calcd for $C_{35}H_{30}N_2O_4S_2Cl_2$: C, 62.03; H, 4.46; N, 4.13; S, 9.46; Cl, 10.46. Found: C, 62.19; H, 4.60; N, 4.19; S, 9.34; Cl, 10.75.

(±)-4-{2-[(3-{4-Chlorophenylsulfonylamino}-1-{3-[(*E*)-2-(7-chloro-2-quinolyl)vinyl]phenyl}propyl)thio]ethyl}benzoic Acid (7h) The title compound was prepared from **6h** in the same manner as described above, and obtained as a pale yellow amorphous solid. (70%). ^{1}H-NMR ($CDCl_3$) δ: 1.95—2.09 (2H, m), 2.51—2.65 (2H, m), 2.73—2.87 (2H, m), 2.92—3.05 (2H, m), 3.84 (1H, t, J=7.6 Hz), 4.93 (1H, t, J=6.4 Hz), 7.14—7.20 (3H, m), 7.34 (1H, t, J=7.6 Hz), 7.42—7.51 (6H, m), 7.62—7.76 (5H, m), 7.96—7.99 (2H, m), 8.10—8.13 (2H, m). FAB-MS m/z: 677 $[M+H]^+$. *Anal.* Calcd for $C_{35}H_{30}N_2O_4S_2Cl_2\cdot 0.1H_2O$: C, 61.87; H, 4.48; N, 4.12; S, 9.44; Cl, 10.44. Found: C, 61.57; H, 4.52; N, 4.11; S, 9.55; Cl, 10.53.

(±)-3-[(2-{4-Chlorophenylsulfonylamino}-1-{3-[(*E*)-2-(7-chloro-2-quinolyl)vinyl]phenyl}ethyl)thio]propanoic Acid (18a) The title compound was prepared from **17a** in the same manner as described above, and obtained as a pale yellow amorphous solid. (59%). ^{1}H-NMR ($CDCl_3$) δ: 2.38—2.71 (4H, m), 3.31—3.38 (2H, m), 4.02 (1H, t, J=7.6 Hz), 6.99—7.78 (13H, m), 8.04—8.17 (2H, m). FAB-MS m/z: 587 $[M+H]^+$. *Anal.* Calcd for $C_{28}H_{24}N_2O_4S_2Cl_2\cdot 0.3H_2O$: C, 56.72; H, 4.18; N, 4.72; S, 10.82; Cl, 11.96. Found: C, 57.60; H, 4.25; N, 5.01; S, 10.85; Cl, 12.04.

(±)-4-[(2-{4-Chlorophenylsulfonylamino}-1-{3-[(*E*)-2-(7-chloro-2-quinolyl)vinyl]phenyl}ethyl)thio]3,3-dimethylbutylic Acid (18b) The title compound was prepared from **17b** in the same manner as described above, and obtained as a pale yellow solid. (31%). mp 177—179 °C. ^{1}H-NMR (DMSO-d_6) δ: 0.98 (6H, s), 2.11—2.19 (2H, m), 2.43—2.55 (2H, m), 3.26—3.35 (2H, m), 3.90 (1H, t, J=7.6 Hz), 7.22—8.03 (13H, m), 8.42 (1H, d, J=8.4 Hz), 12.02 (1H, br s). FAB-MS m/z: 629 $[M+H]^+$. *Anal.* Calcd for $C_{31}H_{30}N_2O_4S_2Cl_2$: C, 59.14; H, 4.80; N, 4.45; S, 10.19; Cl, 11.26. Found: C, 58.75; H, 4.65; N, 4.38; S, 10.29; Cl, 11.37.

(±)-1-{[(2-{4-Chlorophenylsulfonylamino}-1-{3-[(*E*)-2-(7-chloro-2-quinolyl)vinyl]phenyl}ethyl)thio]methyl}cyclopropylacetic Acid (18c) The title compound was prepared from **17c** in the same manner as described above, and obtained as a pale yellow solid. (45%). mp 173—176ºC. ^{1}H-NMR (DMSO-d_6) δ: 0.36—0.44 (4H, m), 2.21—2.33 (2H, m), 2.50—2.58 (2H, m), 3.25—3.35 (2H, m), 3.97 (1H, t, J=7.2 Hz), 7.21—8.03 (14H, m), 8.42 (1H, d, J=8.4 Hz), 12.02 (1h, br s). FAB-MS m/z: 627 $[M+H]^+$. *Anal.* Calcd for $C_{31}H_{28}N_2O_4S_2Cl_2$: C, 59.33; H, 4.50; N, 4.46; S, 10.22; Cl, 11.30. Found: C, 58.94; H, 4.45; N, 4.45; S, 10.06; Cl, 11.22.

(±)-4-{[(2-{4-Chlorophenylsulfonylamino}-1-{3-[(*E*)-2-(7-chloro-2-quinolyl)vinyl]phenyl}ethyl)thio]methyl}benzoic Acid (18d) The title compound was prepared from **17d** in the same manner as described above, and obtained as a pale yellow solid. (55%). mp 188—190 °C. ^{1}H-NMR (DMSO-d_6) δ: 3.23—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), 7.15—8.04 (18H, m), 8.42 (1H, d, J=8.4 Hz), 12.91 (1H, br s). FAB-MS m/z: 649 $[M+H]^+$. *Anal.* Calcd for $C_{33}H_{26}N_2O_4S_2Cl_2$: C, 61.01; H, 4.03; N, 4.31; S, 9.87; Cl, 10.91. Found: C, 60.92; H, 3.97; N, 4.49; S, 9.83; Cl, 10.88.

(±)-4-{[(2-{4-Chlorophenylsulfonylamino}-1-{3-[(*E*)-2-(7-chloro-2-quinolyl)vinyl]phenyl}ethyl)thio]methyl}phenylacetic Acid (18e) The title compound was prepared from **17e** in the same manner as described above, and obtained as a pale yellow solid. (32%). mp 138—140 °C. ^{1}H-NMR (DMSO-d_6) δ: 3.30—3.33 (2H, m), 3.57—3.60 (3H, m), 3.69 (1H, d, J=12.4 Hz), 3.88 (1H, t, J=7.4 Hz), 7.01—8.04 (18H, m), 8.42 (1H, d, J=8.2 Hz). FAB-MS m/z: 663 $[M+H]^+$. *Anal.* Calcd for $C_{34}H_{28}N_2O_4S_2Cl_2$: C, 61.54; H, 4.25; N, 4.22; S, 9.66; Cl, 10.68. Found: C, 61.61; H, 4.31; N, 4.46; S, 9.63; Cl, 10.64.

(±)-4-{[(2-{4-Chlorophenylsulfonylamino}-1-{3-[(*E*)-2-(7-chloro-2-quinolyl)vinyl]phenyl}ethyl)thio]2-ethyl}benzoic Acid (18f) The title compound was prepared from **17f** in the same manner as described above, and obtained as a pale yellow solid. (32%). mp 186—187 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.65—2.87 (4H, m), 3.33 (2H, t, J=7.0 Hz), 3.81 (1H, t, J=7.6 Hz), 4.70—4.72 (1H, m), 7.13—7.75 (14H, m), 7.95—8.15 (5H, m). FAB-MS m/z: 663 $[M+H]^+$. *Anal.* Calcd for $C_{34}H_{28}N_2O_4S_2Cl_2$: C, 61.54; H, 4.25; N, 4.22; S, 9.66; Cl, 10.68. Found: C, 61.61; H, 4.31; N, 4.46; S, 9.63; Cl, 10.64.

(±)-4-{[(2-{Phenylsulfonylamino}-1-{3-[(*E*)-2-(7-chloro-2-quinolyl)-vinyl]phenyl}ethyl)thio]methyl}benzoic Acid (18g) The title compound was prepared from **17g** in the same manner as described above, and obtained as a pale yellow solid. (58%). mp 212—214 °C. ^{1}H-NMR (DMSO-d_6) δ: 3.19—3.36 (2H, m), 3.67 (1H, d, J=13.6 Hz), 3.79 (1H, d, J=13.6 Hz), 3.85—3.89 (1H, m), 6.85—8.12 (19H, m), 8.42 (1H, d, J=8.4 Hz), 12.90 (1H, br s). FAB-MS m/z: 615 $[M+H]^+$. *Anal.* Calcd for $C_{33}H_{27}N_2O_4S_2Cl\cdot 0.1H_2O$: C, 64.24; H, 4.44; N, 4.54; S, 10.39; Cl, 5.75. Found: C, 64.07; H, 4.26; N, 4.63; S, 10.25; Cl, 5.71.

(±)-4-{[(2-{4-Bromophenylsulfonylamino}-1-{3-[(*E*)-2-(7-chloro-2-quinolyl)vinyl]phenyl}ethyl)thio]methyl}benzoic Acid (18h) The title compound was prepared from **17h** in the same manner as described above, and obtained as a pale yellow solid. (69%). mp 203—205 °C. ^{1}H-NMR (DMSO-d_6) δ: 3.23—3.36 (2H, m), 3.78 (1H, d, J=13.6 Hz), 3.80 (1H, d, J=13.6 Hz), 3.86 (1H, t, J=7.6 Hz), 7.15—8.04 (18H, m), 8.42 (1H, d, J=8.8 Hz), 12.92 (1H, br s). FAB-MS m/z: 693 $[M+H]^+$. *Anal.* Calcd for $C_{33}H_{26}N_2O_4S_2ClBr$: C, 57.11; H, 3.78; N, 4.04; S, 9.24; Br, 11.51; Cl, 5.11. Found: C, 57.13; H, 3.68; N, 4.16; S, 9.14; Br, 11.45; Cl, 5.10.

(±)-4-{[(2-{4-Nitrophenylsulfonylamino}-1-{3-[(*E*)-2-(7-chloro-2-quinolyl)vinyl]phenyl}ethyl)thio]methyl}benzoic Acid (18i) The title compound was prepared from **17i** in the same manner as described above, and obtained as a pale yellow solid. (63%). mp 233—235 °C. ^{1}H-NMR (DMSO-d_6) δ: 3.32—3.42 (2H, m), 3.68 (1H, d, J=13.6 Hz), 3.81 (1H, d, J=13.6 Hz), 3.86 (1H, t, J=6.4 Hz), 7.15—8.04 (14H, m), 8.28—8.43 (5H, m), 12.91 (1H, br s). FAB-MS m/z: 660 $[M+H]^+$. *Anal.* Calcd for $C_{33}H_{26}N_3O_6S_2Cl$: C, 60.04; H, 3.97; N, 6.37; S, 9.71; Cl, 5.37. Found: C, 59.91; H, 3.98; N, 6.33; S, 9.65; Cl, 5.40.

(±)-4-{[(2-{4-Fluorophenylsulfonylamino}-1-{3-[(*E*)-2-(7-chloro-2-quinolyl)vinyl]phenyl}ethyl)thio]methyl}benzoic Acid (18j) The title compound was prepared from **17j** in the same manner as described above, and obtained as a pale yellow solid. (74%). mp 192—193 °C. ^{1}H-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), 3.88 (1H, t, J=7.2 Hz), 7.12—8.04 (18H, m), 8.42 (1H, d, J=8.4 Hz), 12.91 (1H, br s). FAB-MS m/z: 633 $[M+H]^+$. *Anal.* Calcd for $C_{33}H_{26}N_2O_4S_2ClF$: C, 62.60; H, 4.14; N, 4.42; S, 10.13; Cl, 5.60; F, 3.00. 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_2PO_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 gas mixture. The tissue was placed under tension using a 1-g mass. The force generated by the tissue was isometrically measured. The ileum contractile response against 1×10^{-9} 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 $110\times\boldsymbol{g}$ for 10 min to yield PPP. The PRP was diluted with PPP to adjust control of the platelet count 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 (Nikoh 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

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.

LTD_4-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 LTD_4 and the vehicle solution were administered intracutaneously on the back of the guinea pig (at 2 points for LTD_4 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% Na_2SO_4 solution) and the amount of LTD_4-induced pigment leakage was measured using the 620 nm absorbance of the extract (UV-visible spectrophotometer, model UV-160A; Shimadzu, Kyoto). LTD_4-induced dye leakage was defined by subtracting the dye content in the vehicle-injected site from that in the LTD_4-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 LTD_4.

U46619-Induced Increase in Airway Resistance Increase Male Hartley guinea pigs were anesthetized by intraperitoneal injection of 1.2 g/kg urethane and a tracheal cannula was inserted. Spontaneous respiration was stopped with gallamine (1 mg/kg i.v.), and artificial respiration was carried out at a rate of 60 strokes/min and a volume of 1 ml/100 g body weight per cycle. After intravenous administration of U46619 (3 μg/kg), airway resistance was measured using a respiratory function measuring apparatus (Model 6; Buxco 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 injection 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.
2) Wenzel S. E., *Pharmacotherapy*, **17**, 3S—12S (1997).
3) Francis H. P., Greenham S. J., Patel U. P., Thompson A. M., Gardiner P. J., *Br. J. Pharmacol.*, **104**, 596—602 (1991).
4) Jones G. L., Saroea H. G., Watson R. M., O'byrne P. M., *Am. Rev. Respir. Dis.*, **145**, 1270—1274 (1992).
5) Rinkema L. E., Bemis K. G., Fleisch J. H., *J. Pharmacol. Exp. Ther.*, **230**, 550—557 (1984).
6) Ueno A., Tanaka K., Katori M., *Prostaglandins*, **23**, 865—880 (1982).
7) Obata T., Yamashita N., Nakagawa T., *Clinical Reviews in Allergy*, **12**, 79—93 (1994).
8) Fujimura M., Sakamoto S., Saito. M., Miyake Y., Matsuda T., *Allergy Clin. Immunol.*, **87**, 23—27 (1991).
9) Nakagawa N., Obata T., Kobayashi T., Okada Y., Nambu F., Terawaki T., Aishita H., *Jpn. J. Pharmacol.*, **60**, 217—225 (1992).
10) Krell G. D., Aharony D., Buckner C. K., Keith R. A., Kusner E. J., Snyder D. W., Bernstein P. R., Matassa V. G., Yee Y. K., Brown F. J., Hesp B., Giles R. E., *Am. Rev. Respir. Dis.*, **141**, 978—987 (1990).
11) Barnes N. C., Pujet J. C., *Thorax*, **52**, 523—527 (1997).
12) Taniguchi Y., Tamura G., Honma M., Aizawa T., Murayama N., Shirato K., Takishima T., *J. Allergy Clin. Immunol.*, **92**, 507—512 (1993).
13) Adkins J. C., Brogden R. N., *Drugs*, **55**, 121—144 (1998).
14) Samara E., Cao G., Locke C., Grannerman G. R., Dean R., Killian A., *Clin. Pharmacol. Ther.*, **62**, 426—435 (1997).
15) Kurashima K., Ogawa H., Ohka T., Fujimura M., Matsuda T., *Ann. Allergy*, **68**, 53—56 (1992).
16) Yamada T., Takahashi Y., Ishizaki M., Musoh K., Ohashi T., Tanaka H., Inagaki N., Nagai H., *Pharmacology*, **69**, 51—58 (2003).
17) Arakida Y., Suwa K., Ohga K., Yokota M., Miyata K., Yamada T., Honda K., *J. Pharmacol. Exp Ther.*, **287**, 633—639 (1998).
18) Arakida Y., Ohga K., Kobayashi S., Yokota M., Miyata K., Yamada T., Honda K., *Eur. J. Pharm.*, **362**, 229—233 (1998).
19) Arakida Y., Ohga K., Suwa K., Yokota M., Miyata K., Yamada T., Honda K., *J. Pharmacol. Exp Ther.*, **290**, 1285—1291 (1999).
20) Arakida Y., Ohga K., Okada Y., Morio H., Suwa K., Yokota M., *Eur. J. Pharm.*, **403**, 169—179 (2000).
21) Arakida Y., Ohga K., Suwa K., Okada Y., Morio H., Yokota M., Miyata K., Yamada T., Honda K., *Jpn. J. Pharmacol.*, **82**, 287—294 (2000).
22) Arakida Y., Ohga K., Suwa K., Okada Y., Morio H., Yokota M., Mi–yata K., Yamada T., Honda K., *Jpn. J. Pharmacol.*, **83**, 63—72 (2000).
23) Jones T. R., Labelle M., Belly M., Champion E., Charette L., Evans J., Ford-Hutchinson A. W., Gauthier J. Y., Lord A., Masson P., Mcauliffe M., Mcfarlane C. S., Matters K. M., Pickett C., Piechuta H., Rochette C., Rodger I. W., Sawyer N., Young R. N., Zamboni R., Abraham W. M., *Can. J. Pharmacol.*, **73**, 191—201 (1995).
24) Mais D. E., Mohamadi F., Dubé G. P., Kurtz W. L., Brune K. A., Utterback B. G., Spees M. M., Jakubowski J. A., *Eur. J. Med. Chem.*, **26**, 821—827 (1991).
25) King A. O., Corley E. G., Anderson R. D., Larsen T. R., Verhoeven T. R., Reider P. J., *J. Org. Chem.*, **58**, 3731—3735 (1993).
26) McNamara J. J., Leazer J. L., Bhupathy M., Amato J. S., Reamer R. A., Reider P. J., Grabowski E. J. J., *J. Org. Chem.*, **54**, 3718—3725 (1989).