Piperidineacrylate Derivatives as Potential Antiallergy Agents

Mitsuo SUGIYAMA,*,[a] Toshiaki SAKAMOTO,[a] Yumiko KAMIGAKI,[a] Hiroshi FUKUMI,[a] Kazuhiro ITOH,[b] Yumiko SATOH,[b] and Takeshi YAMAGUCHI[b]

Medicinal Chemistry Research Laboratories[a] and Biological Research Laboratories,[b] Sankyo Co., Ltd., 1–2–58 Hiromachi, Shinagawa-ku, Tokyo 140, Japan. Received September 8, 1992

A new series of piperidineacrylate derivatives was prepared and evaluated for antiallergic activity. Most of the compounds showed potent activities in the rat passive cutaneous anaphylaxis (PCA) assay. In particular, ethyl 1-[2-bis(4-fluorophenyl)methoxyethyl]-4-piperidineacrylate (1a) was more potent than oxatomide and terfenadine in this assay, and was selected for further study. Some pharmacological properties of 1a are presented.

Keywords antiallergic agent; piperidineacrylate; structure–activity relationship; anti-passive cutaneous anaphylaxis activity; IgG_1-mediated bronchoconstriction inhibitory activity

Several chemical mediators including histamine, leukotrienes, prostaglandins, and serotonin are produced by mast cells, basophils, and eosinophils. The release of these mediators upon exposure to antigen has been implicated in the pathogenesis of asthma and other allergic diseases.[1] Thus, many drugs which are currently applied as antiallergic agents act as antagonists of these chemical mediators. On the other hand, the generalized inhibition of mediator release is becoming an increasingly attractive approach for the development of new antiallergic drugs and, following this approach, several drugs have been found which inhibit mediator release, although the modes of action of these drugs have not been elucidated.[2]

In order to discover novel, potent, and orally active drugs for the treatment of allergic diseases, we have synthesized many compounds and tested their efficacies by using the rat passive cutaneous anaphylaxis (PCA) assay. In particular, we found that compound I, a benzhydryloxyethylpiperidine derivative bearing a fluorine atom at the 4-position of each benzene ring, possesses a considerable antiallergic activity.[3] Antiallergic activity was found for I at 1.4 mg/kg in the PCA assay, and structural modification of I led to a series of 1-[2-bis(4-fluorophenyl)methoxyethyl]-4-piperidineacrylate derivatives (**1**). The synthesis and biological evaluation of these compounds are described in this paper.

Chemistry

The piperidineacrylate **1a** was prepared from bis(4-fluorophenyl)methyl 2-chloroethyl ether (**2**)[4] according to Chart 1. The treatment of **2** with 4-hydroxypiperidine followed by Swern oxidation of the secondary alcohol intermediate provided 1-[2-bis(4-fluorophenyl)methoxyethyl]-4-piperidone (**3**) in 60% yield. The Wittig reaction of **3** with methoxymethylene triphenylphosphorane followed by acidic hydrolysis gave the aldehyde **4a** in 42% yield. Subsequently, the reaction of **4a** with triethyl phosphonoacetate and sodium hydride (NaH) gave **1a** in 91% yield. Compound **1a** was assigned the *E*-configuration on the basis of coupling constants for the olefinic protons (15.6 Hz) in the NMR spectrum. A convenient alternative synthetic method for **1a** was also examined. *N*-Substituted piperidinecarboxylate (**5**) and cyanopiperidine (**6a**) were obtained by the treatment of **2** with piperidinecarboxylate and cyanopiperidine,[5] respectively. Reduction of **6a** or **5** with diisobutylaluminum hydride (DIBAL) gave **4a** in moderate yields. These procedures provided facile and practical methods for the preparation of substituted piperidineacrylate derivatives.

The general synthetic pathway for the preparation of piperidineacrylates **1b—e**, **h—k** is shown in Chart 2.

The R_1-substituted piperidineacrylates **1b—d** were prepared by Horner–Emmons reaction of **4a** with triethyl

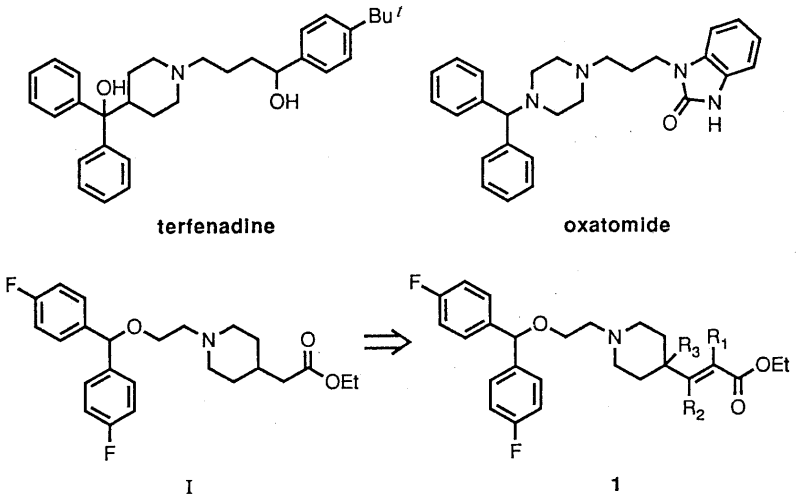


Fig. 1

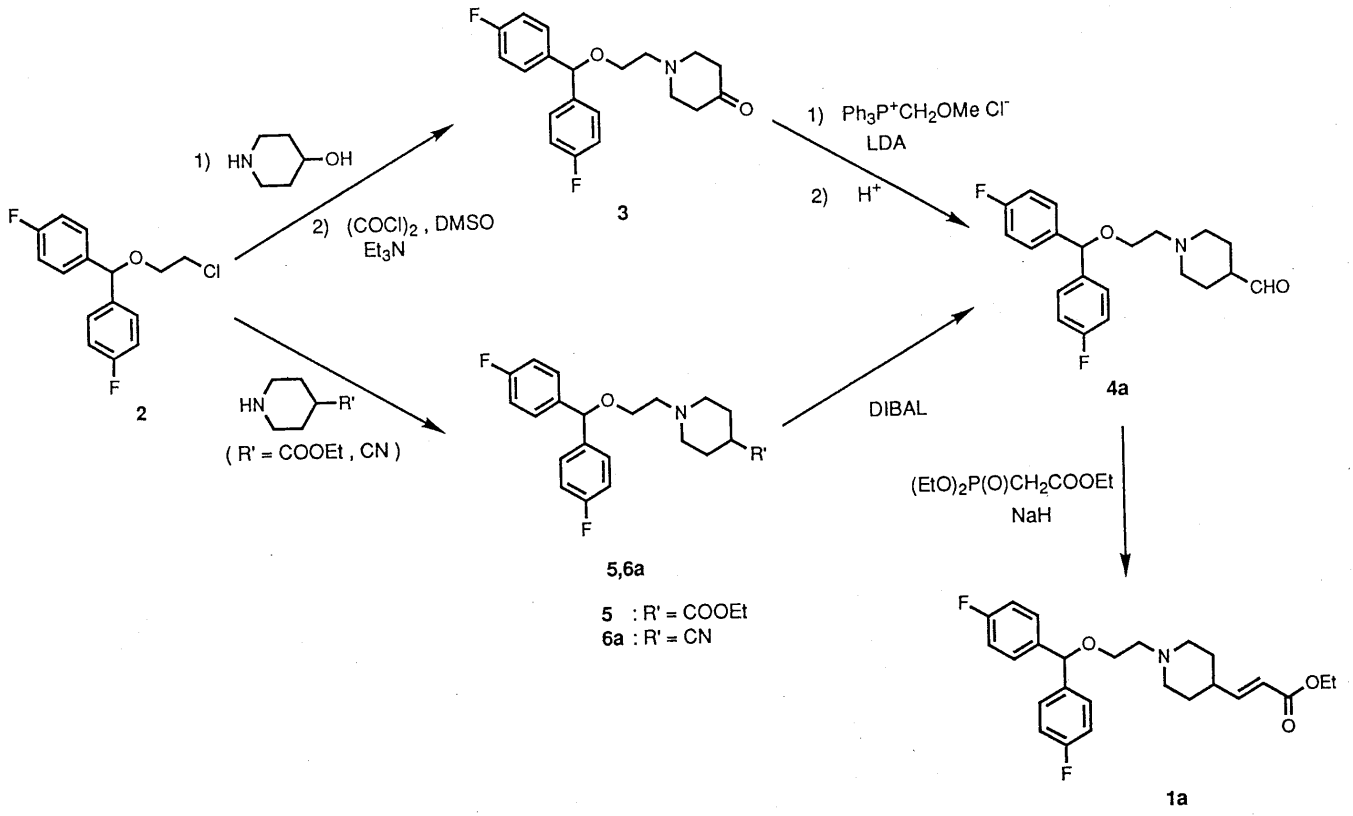


Chart 1

2-phosphonopropionate or by condensation of **4a** with various esters bearing an active methylene. In these reactions, the Horner–Emmons reaction of **4a** with triethyl 2-phosphonopropionate yielded **1b** with an $E:Z$ ratio of 1:2 as determined by its NMR spectrum.

Attempts to introduce substituents at the R_2 position using **6a** and Grignard reagents were unsuccessful. These failures led us to investigate an alternative synthetic route. Treatment of the piperidinecarboxylate **5** with lithium diisopropylamide (LDA) and acetaldehyde (or citronellal) followed by oxidation afforded the β-ketoesters **8e, f**, which were decarboxylated to give **9e, f** according to Krapcho's method.[6] Compound **9g** was prepared starting from **2**. Although Horner–Emmons reaction of **9e** afforded the piperidineacrylate **1e** in 57% yield, condensation of **9f, g** with triethyl phosphonoacetate was not observed. Why these condensations did not proceed is not clear, but the decreased reactivities of **9f, g** as compared with that of **9e** might be explained by steric hindrance of the substituent R_2.

R_3-Substituted piperidineacrylates **1i—k** were prepared according to Chart 2. 4-Methyl- or 4-benzyl-4-cyanopiperidine derivatives **6i, j** were obtained by lithiation of **6a** with LDA followed by methylation or benzylation. The 4-phenyl derivative **6k** was prepared by the reaction of **2** with 4-cyano-4-phenylpiperidine. Reduction of **6i—k** with DIBAL gave the aldehyde derivatives **4i—k**, which were condensed with triethyl phosphonoacetate to form the corresponding piperidineacrylates **1i—k**.

The diester derivative **1h**, which has a ester group at R_3, was prepared by the treatment of **8e** with the triethyl phosphonoacetate.

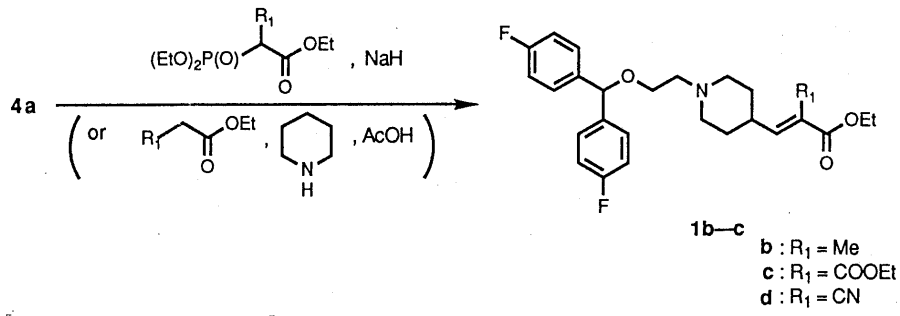
Benzhydryl 2-chloroethyl ether[4] and (4-chlorophenyl)phenylmethyl 2-chloroethyl ether[4] were employed in a synthesis similar to that depicted in Chart 1 to yield **10a** and **10b**, respectively. The fluorine atom at the 4-position of each benzene ring in **1a** was replaced by either a hydrogen atom or a chlorine atom and the pharmacological activities of the resulting piperidineacrylate derivatives **10a, b** were compared with that of **1a**. The physical properties of **1** and **10** are summarized in Table I.

Pharmacological Results and Discussion

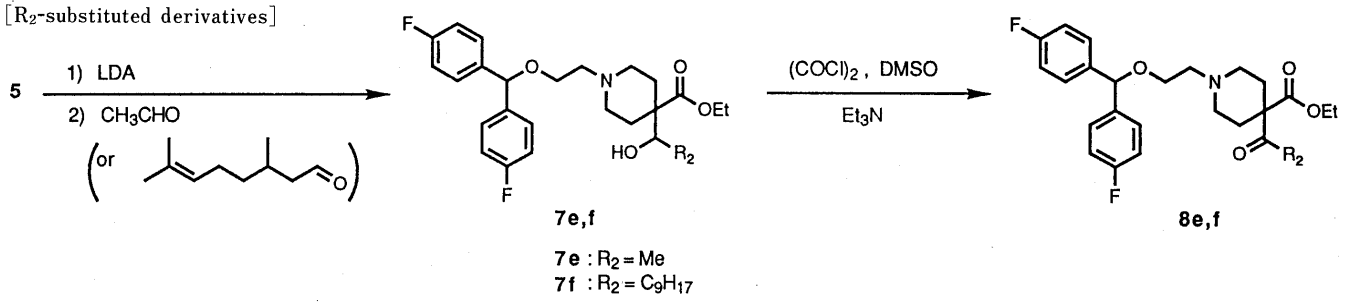
Compounds **1**, **10**, and the reference compounds, terfenadine and oxatomide, were orally administered and evaluated for antiallergic activity by using the PCA assay.

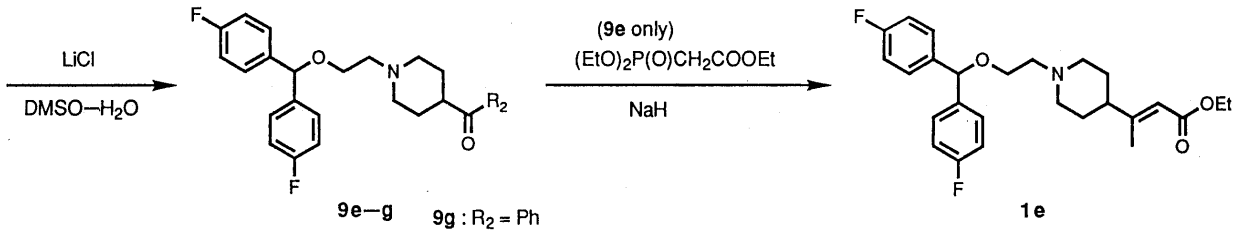
As can be seen in Table I, the inhibitory activities of compounds **1a—e**, **h—k** were more potent than that of oxatomide and were almost equipotent to that of terfenadine. The introduction of halogen into the benzene ring resulted in increased activity in comparison with the unsubstituted derivative (**10a**). Compound **1a** having 4-F substituents of both benzene rings was the most active among these compounds (**1a**, **10a, b**). We next examined the influence of the introduction of substituents into the acrylate moiety. Compounds **1b—d** bearing substituents on R_1 showed somewhat weaker PCA inhibitory activity than **1a**. The substituents of R_2 had no significant influence on the inhibitory activity (**1e, h**), while the introduction of large substituents into R_3 led to increased antiallergic activity (**1j**). Based on these findings, compounds **1a** and **1j** were selected for further investigation. Their inhibitory activities on the PCA assay of **1a, j** are more potent than those of other reference drugs. Compound **1a** was about 5 times as potent as terfenadine in the inhibition of IgG_1-mediated bronchoconstriction. Although compound **1j** was somewhat

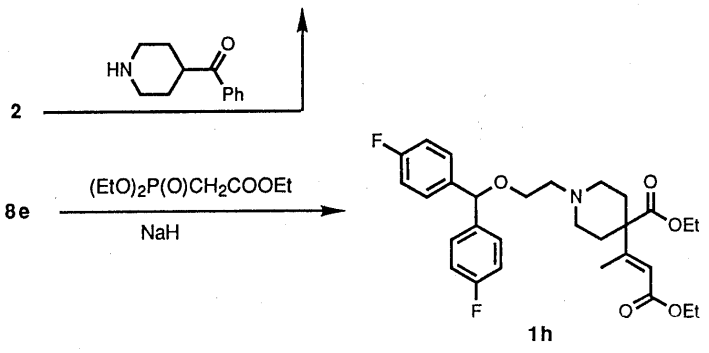
[R_1-substituted derivatives]



[R_2-substituted derivatives]







[R_3-substituted derivatives]

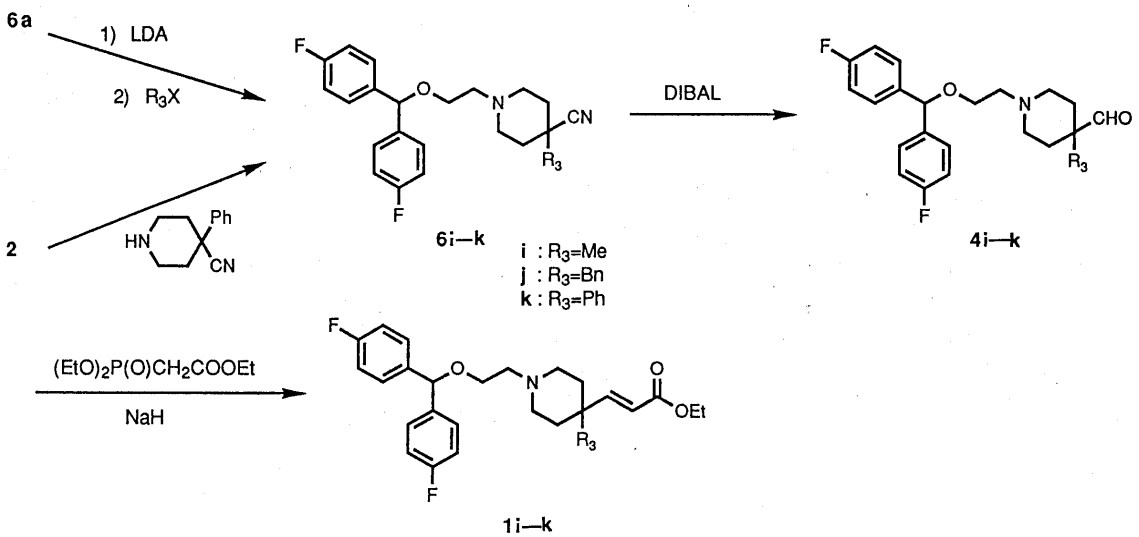
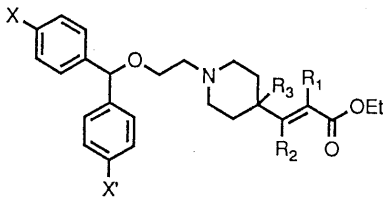


Chart 2

TABLE I. Substituted Piperidineacrylate Derivatives



1, 10

Compd.[a] No.	X	X′	R_1	R_2	R_3	Yield (%)	Formula	mp (°C) (Recryst. solvent)[b]	Analysis (%) Calcd (Found) C	H	N	F(Cl)	PCA assay[c] Inhibition % (3.2 mg/kg *p.o.*) (ID_{50}, mg/kg)
1a	F	F	H	H	H	91	$C_{25}H_{29}F_2NO_3 \cdot C_2H_2O_4$	142—143 (E–EA)	62.42 (62.58	6.01 6.16	2.70 2.80	7.31 7.19)	52.2± 5.5 (3.1)
1b[d]	F	F	Me	H	H	Quant.	$C_{26}H_{31}F_2NO_3 \cdot C_4H_4O_4$	108—110 (M–EE)	64.39 (64.43	6.30 6.47	2.50 2.53	6.79 6.78)	48.5± 9.2
1c	F	F	COOEt	H	H	89	$C_{28}H_{33}F_2NO_5 \cdot C_4H_4O_4 \cdot 1/2H_2O$	112—113 (EA)	61.33 (61.62	6.11 6.18	2.24 2.25	6.06 6.02)	10.0±16.1
1d	F	F	CN	H	H	81	$C_{26}H_{28}F_2N_2O_3 \cdot C_4H_4O_4$	143—144 (EA)	63.15 (62.86	5.65 5.64	4.91 4.92	6.66 6.65)	36.0±13.7
1e	F	F	H	Me	H	57	$C_{26}H_{31}F_2NO_3 \cdot C_4H_4O_4$	143—145 (M–EE)	64.39 (64.67	6.30 6.32	2.50 2.62	6.79 6.99)	41.5±14.1
1h	F	F	H	Me	COOEt	37	$C_{29}H_{35}F_2NO_5 \cdot C_4H_4O_4$	154—156 (M–EE)	62.75 (62.73	6.22 6.23	2.22 2.14	6.02 5.78)	47.0±15.0
1i	F	F	H	H	Me	88	$C_{26}H_{31}F_2NO_3 \cdot C_4H_4O_4$	159—161 (M–EE)	64.39 (64.51	6.30 6.39	2.50 2.73	6.79 6.83)	41.8±13.8
1j	F	F	H	H	Bn	76	$C_{32}H_{35}F_2NO_3 \cdot C_4H_4O_4$	170—171 (M–EE)	68.02 (68.01	6.18 6.17	2.20 2.43	5.98 6.00)	70.1± 2.7 (1.6)
1K	F	F	H	H	Ph	72	$C_{31}H_{33}F_2NO_3 \cdot C_2H_2O_4$	143—147 (M–EA)	66.54 (66.62	5.92 6.13	2.35 2.50	6.38 6.55)	58.1± 6.4 (1.7)
10a	H	H	H	H	H	49	$C_{25}H_{31}NO_3 \cdot C_2H_2O_4 \cdot 1/3H_2O$	145—147 (E–EA)	66.24 (66.24	6.93 6.83	2.86 2.81)		21.9±11.8 (7.0)
10b	H	Cl	H	H	H	Quant.	$C_{25}H_{30}ClNO_3 \cdot C_2H_2O_4$	148—150 (E–EA)	62.60 (62.80	6.23 6.38	2.70 2.68	6.84 6.82)	31.5±16.0 (6.7)
Oxatomide													28.2± 4.4 (11.2)
Terfenadine													37.7± 8.4 (5.7)

a) All compounds were obtained as fumaric acid salts, except **1a**, **k**, **10a**, and **10b** (oxalic acid salts). *b*) E, EtOH; EA, AcOEt; EE, Et_2O; M, MeOH. *c*) Percent inhibition ± standard error of the PCA assay. Each value represents the mean of four rats. *d*) *E*:*Z* ratio is 1:2.

TABLE II. Comparative Pharmacological Data for Compounds **1a** and **1j**

Compound No.	PCA assay ID_{50}, mk/kg, *p.o.* (95% C.L.)	Bronchoconstriction ED_{50}, mg/kg, *p.o.* (95% C.L.)	Histamine release inhibition (%, mg/kg, *p.o.*)	SRS-A release inhibition IC_{50}, μg/ml (95% C.L.)
1a	3.1 (1.9—7.2)	0.049 (0.007—0.35)	63.4 (25)[a]	57.4 (40.0—82.4)
1j	1.6 (0.64—3.8)	>0.1 (20%)	NT[b]	>80 (17%)
Oxatomide	11.2 (6.6—19.0)	1.6 (0.50—5.3)	42.8 (50)[a]	31.3 (19.2—51.2)
Terfenadine	5.7 (3.4—9.7)	0.26 (0.12—0.56)	2.3 (25)	30.3 (21.0—43.7)

a) $p<0.01$. *b*) Not tested.

more potent than **1a** in the PCA assay, this compound (**1j**) did not exhibit a significant increase in the bronchoconstriction inhibitory activity. Furthermore, compound **1a** remarkably inhibited histamine release compared with other drugs.

Further studies on the synthesis and structure–activity relationship of piperidineacrylate derivatives as antiallergic agents are in progress.

Experimental

Melting points are uncorrected. IR spectra were recorded on a JASCO A-2 spectrometer and ^{1}H-NMR spectra on a Varian EM-390L spectrometer (90 MHz), or a JEOL GX-270 spectrometer (270 MHz) using Me_4Si as an internal standard. MS were obtained on a JEOL JMS D300 spectrometer. Column chromatography was performed on silica gel (Kieselgel 60 Art. 7734, 60-230 mesh, E. Merck). The developing solvents are shown in parentheses. The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; dd, doublet of doublets; dt, doublet of triplets; m, multiplet; br, broad.

1-[2-Bis(4-fluorophenyl)methoxyethyl]-4-piperidone (3) A mixture of **2** (14.1 g, 50.0 mmol), 4-hydroxypiperidine (5.10 g, 50.4 mmol), Na_2CO_3 (12.0 g, 113 mmol), and a catalytic amount of NaI (0.2 g) in 4-methyl-2-pentanone (200 ml) was refluxed for 9 h and then cooled. Insoluble material was filtered off, the filtrate was concentrated *in vacuo*, and the residue was chromatographed on silica gel (EtOH–CH_2Cl_2, 1:9) to give 1-[2-bis(4-fluorophenyl)methoxyethyl]-4-piperidinol (11.50 g, 66%)

as an oil. IR ($CHCl_3$) cm^{-1}: 2930, 1600, 1505. ^1H-NMR (90 MHz, $CDCl_3$) δ: 1.36—2.07 (4H, m), 2.07—2.42 (2H, m), 2.65 (2H, t, $J=5.8$ Hz), 2.64—2.95 (2H, m), 3.58 (2H, t, $J=5.8$ Hz), 3.55—3.90 (1H, m), 5.36 (1H, s), 6.89—7.17 (4H, m), 7.20—7.45 (4H, m). MS m/z: 347 (M^+), 114.

A solution of dimethylsulfoxide (DMSO) (11.3 ml, 159 mmol) in anhydrous CH_2Cl_2 (36 ml) was added to a stirred solution of oxalyl chloride (6.63 ml, 76.0 mmol) in anhydrous CH_2Cl_2 (160 ml) at -60 °C over a period of 30 min under an N_2 atmosphere. The reaction mixture was stirred for 15 min at the same temperature, then a solution of the piperidinol (11.5 g, 33.1 mmol) in anhydrous CH_2Cl_2 (33 ml) was added dropwise to this mixture at the same temperature over a period of 20 min. Stirring was continued for an additional 30 min at -60 °C, then Et_3N (46 ml, 332 mmol) was added and the whole was warmed to room temperature. The reaction was quenched with H_2O and the mixture was extracted with CH_2Cl_2. The residue obtained from the extracts was purified by column chromatography on silica gel (AcOEt–CH_2Cl_2, 1:9) to give **3** (10.23 g, 91%) as an oil. *Anal.* Calcd for $C_{20}H_{21}F_2NO_2$: C, 69.55; H, 6.13; N, 4.06; F, 11.00. Found: C, 69.71; H, 5.99; N, 4.03; F, 10.87. IR ($CHCl_3$) cm^{-1}: 2955, 2900, 2800, 1720 (sh), 1700, 1605, 1500. ^1H-NMR (90 MHz, $CDCl_3$) δ: 2.33—2.57 (4H, m), 2.69—2.93 (6H, m), 3.60 (2H, t, $J=5.8$ Hz), 5.35 (1H, s), 6.86—7.17 (4H, m), 7.20—7.43 (4H, m). MS m/z: 345 (M^+), 112.

1-[2-Bis(4-fluorophenyl)methoxyethyl]-4-methoxymethylenepiperidine A solution of LDA [prepared from 1.6 M *n*-BuLi in hexane (12.0 ml, 19.2 mmol) and diisopropylamine (1.93 g, 19.1 mmol)] in anhydrous tetrahydrofuran (THF) (15 ml) was added dropwise to a suspension of (methoxymethyl)triphenylphosphonium chloride (4.80 g, 14.0 mmol) in anhydrous THF (25 ml) at -10 °C (ice–acetone bath) during 20 min under an N_2 atmosphere. The reaction mixture was stirred for 30 min at the same temperature, then a solution of **3** (4.40 g, 12.7 mmol) in anhydrous THF (20 ml) was slowly added to this mixture over 20 min and the reaction mixture was warmed to room temperature. Stirring was continued for an additional 16 h at the same temperature, then the mixture was quenched with saturated aqueous NH_4Cl solution, poured into brine, and extracted with AcOEt. The residue obtained from the AcOEt extracts was purified by column chromatography on silica gel (AcOEt–hexane, 2:1) to give the title compound (3.37 g, 71%) as an oil. *Anal.* Calcd for $C_{22}H_{25}F_2NO_2$: C, 70.76; H, 6.75; N, 3.75; F, 10.17. Found: C, 70.47; H, 6.84; N, 3.66; F, 10.05. IR ($CHCl_3$) cm^{-1}: 2945, 2900 (sh), 2840, 1690, 1605, 1500. ^1H-NMR (90 MHz, $CDCl_3$) δ: 1.93—2.87 (8H, m), 2.66 (2H, t, $J=6.1$ Hz), 3.54 (3H, s), 3.57 (2H, t, $J=6.1$ Hz), 5.35 (1H, s), 5.79 (1H, br s), 6.89—7.13 (4H, m), 7.20—7.44 (4H, m). MS m/z: 374 ($M^+ + 1$), 140.

1-[2-(Bis(4-fluorophenyl)methoxyethyl]-4-piperidinecarbaldehyde (4a) (a) A solution of the methoxymethylenepiperidine derivative (2.92 g, 7.82 mmol) in THF (20 ml) was added to 10% aqueous HCl solution (10 ml) and the whole was stirred for 2 h at room temperature. The reaction mixture was basified with saturated aqueous $NaHCO_3$ solution and extracted with AcOEt. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*, and the resulting oily residue was chromatographed on silica gel (MeOH–CH_2Cl_2, 3:97) to give **4a** (1.67 g, 59%) as an oil. IR ($CHCl_3$) cm^{-1}: 2950, 1725, 1605, 1510. ^1H-NMR (90 MHz, $CDCl_3$) δ: 1.40—3.07 (11H, m), 2.63 (2H, t, $J=6.0$ Hz), 3.53 (2H, t, $J=6.0$ Hz), 5.32 (1H, s), 6.82—7.50 (8H, m), 9.70 (1H, s). MS m/z: 360 ($M^+ + 1$), 126.

(b) A 1 M DIBAL solution in hexane (80 ml, 80 mmol) was added dropwise to a stirred solution of **5** (29.02 g, 71.9 mmol) in anhydrous toluene (300 ml) at -60 °C over a period of 75 min under an N_2 atmosphere. The reaction mixture was stirred for 1 h at the same temperature, then the reaction was quenched with MeOH (20 ml) and saturated aqueous NH_4Cl solution (30 ml) and the whole was stirred for an additional 1 h at room temperature. The resulting precipitate was collected by filteration through Celite and the filtrate was extracted with toluene. The residue obtained from the extracts was chromatographed on silica gel (AcOEt) to afford **4a** (19.59 g, 76%) as an oil.

(c) A 1 M DIBAL solution in hexane (75 ml, 75 mmol) was added dropwise to a stirred solution of **6a** (20.25 g, 56.8 mmol) in anhydrous THF (400 ml) at -15 °C over a period of 40 min under an N_2 atmosphere. After being stirred for 15 h at room temperature, the mixture was cooled to 0 °C and the reaction was quenched with MeOH (15 ml) and saturated aqueous NH_4Cl solution (100 ml). The whole was stirred for an additional 1 h at room temperature. The resulting precipitate was removed by filteration through Celite and the filtrate was extracted with AcOEt. The residue obtained from the extracts was chromatographed on silica gel (AcOEt) to afford **4a** (14.67 g, 72%) as an oil.

Ethyl 1-[2-Bis(4-fluorophenyl)methoxyethyl]-4-piperidinecarboxylate (5) A mixture of **2** (10.10 g, 35.7 mmol), ethyl 4-piperidinecarboxylate (6.59 g, 41.1 mmol), Na_2CO_3 (18.92 g, 179 mmol), and a catalytic amount of NaI (0.25 g) in 4-methyl-2-pentanone (60 ml) was refluxed for 17 h and then cooled. Insoluble material was filtered off, the filtrate was concentrated *in vacuo*, and the residue was chromatographed on silica gel (AcOEt–hexane, 1:1) to give **5** (11.59 g, 80%) as an oil. IR ($CHCl_3$) cm^{-1}: 2940, 1725, 1600, 1500. ^1H-NMR (90 MHz, $CDCl_3$) δ: 1.25 (3H, t, $J=7.2$ Hz), 1.72—2.50 (7H, m), 2.62 (2H, t, $J=5.8$ Hz), 2.88 (2H, m), 3.57 (2H, t, $J=5.8$ Hz), 4.13 (2H, q, $J=7.2$ Hz), 5.36 (1H, s), 6.90—7.13 (4H, m), 7.20—7.47 (4H, m). MS m/z: 404 ($M^+ + 1$), 170. The carboxylate **5** formed an oxalic acid salt as colorless prisms. mp (dec.) 145—147 °C. *Anal.* Calcd for $C_{23}H_{27}F_2NO_3 \cdot C_2H_2O_4$: C, 60.84; H, 5.92; N, 2.84; F, 7.70. Found: C, 60.92; H, 6.03; N, 3.01; F, 7.81.

1-[2-Bis(4-fluorophenyl)methoxyethyl]-4-cyanopiperidine (6a) Following a procedure similar to that described for **5**, **6a** was obtained as an oil in 88% yield by treatment of **2** with 4-cyanopiperidine.[5] *Anal.* Calcd for $C_{21}H_{22}F_2N_2O$: C, 70.77; H, 6.22; N, 7.86; F, 10.66. Found: C, 70.77; H, 6.50; N, 7.70; F, 10.64. IR ($CHCl_3$) cm^{-1}: 2950, 2245, 1605, 1510. ^1H-NMR (90 MHz, $CDCl_3$) δ: 1.73—2.08 (4H m), 2.24—2.97 (5H, m), 2.66 (2H, t, $J=5.8$ Hz), 3.54 (2H, t, $J=5.8$ Hz), 5.33 (1H, br s), 6.89—7.17 (4H, m), 7.20—7.45 (4H, m). MS m/z: 357 ($M^+ + 1$), 123.

Ethyl 1-[2-Bis(4-fluorophenyl)methoxyethyl]-4-piperidineacrylate (1a) A solution of triethyl phosphonoacetate (4.01 g, 17.9 mmol) in anhydrous THF (20 ml) was added dropwise to a suspension of NaH (55% in oil dispersion, 870 mg, 19.9 mmol) in anhydrous THF (90 ml) at 0 °C over a period of 5 min under an N_2 atmosphere. Stirring was continued for an additional 30 min at room temperature and then the mixture was cooled to 0 °C. A solution of **4a** (5.85 g, 16.3 mmol) in anhydrous THF (50 ml) was added dropwise over a period of 30 min and the whole was stirred for 1 h at room temperature. The solvent was evaporated under reduced pressure, and the residue was partitioned between AcOEt and brine. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product. This product was purified by column chromatography on silica gel (CH_2Cl_2–MeOH, 19:1) to afford **1a** (6.34 g, 91%) as an oil. IR ($CHCl_3$) cm^{-1}: 2920, 1705, 1645, 1600, 1500. ^1H-NMR (90 MHz, $CDCl_3$) δ: 1.27 (3H, t, $J=7.2$ Hz), 1.46—2.33 (7H, m), 2.63 (2H, t, $J=6.0$ Hz), 2.78—3.07 (2H, m), 3.55 (2H, t, $J=6.0$ Hz), 4.18 (2H, q, $J=7.2$ Hz), 5.34 (1H, s), 5.79 (1H, d, $J=15.6$ Hz), 6.79—7.45 (9H, m). MS m/z: 430 ($M^+ + 1$), 196. Compound **1a** formed an oxalic acid salt as colorless prisms.

Following a procedure similar to that described for **1a**, compounds **1b**, **e**, **h**—**k** were each obtained as oils, by treatment of **4a**, **i**—**k**, **8e**, and **9e** with triethyl phosphonoacetate or triethyl 2-phosphonopropionate.

1b: Yield: 69%. This compound was an *E*- and *Z*-isomeric mixture (*E*:*Z*=1:2). IR ($CHCl_3$) cm^{-1}: 2925, 1700, 1605, 1500. ^1H-NMR (270 MHz, $CDCl_3$) δ: 1.29 and 1.30 (3H, each t, $J=7.1$ Hz), 1.34—1.57 (2H, m), 1.57—1.75 (2H, m), 1.84 ((*E*)-CH_3, d, $J=1.5$ Hz), 1.88 ((*Z*)-CH_3, d, $J=1.3$ Hz), 2.09 (2H, br t, $J=11.7$ Hz), 2.65 (2H, t, $J=6.1$ Hz), 2.83—3.00 (3H, m), 3.56 (2H, t, $J=6.1$ Hz), 4.19 (2H, q, $J=7.1$ Hz), 5.33 (1H, s), 5.71 ((*Z*)-vinyl-H, dd, $J=9.5$, 1.3 Hz), 6.57 ((*E*)-vinyl-H, dd, $J=9.3$, 1.5 Hz), 6.95—7.05 (4H, m), 7.24—7.30 (4H, m). MS m/z: 444 ($M^+ + 1$), 210.

1e: Yield: 57%. IR ($CHCl_3$) cm^{-1}: 2940, 1705, 1640, 1600, 1510. ^1H-NMR (270 MHz, $CDCl_3$) δ: 1.27 (3H, t, $J=7.2$ Hz), 1.44—1.72 (4H, m), 1.88—2.00 (1H, m), 2.06 (2H, dt, $J=11.5$, 2.6 Hz), 2.14 (3H, d, $J=1.5$ Hz), 2.66 (2H, t, $J=6.1$ Hz), 2.94—3.07 (2H, m), 3.56 (2H, t, $J=6.1$ Hz), 4.15 (2H, q, $J=7.2$ Hz), 5.34 (1H, s), 5.65—5.69 (1H, m), 6.97—7.05 (4H, m), 7.24—7.30 (4H, m). MS m/z: 443 (M^+), 210.

1h: Yield: 37%. IR ($CHCl_3$) cm^{-1}: 2950, 1720, 1640, 1605, 1510. ^1H-NMR (270 MHz, $CDCl_3$) δ: 1.23 (3H, t, $J=7.0$ Hz), 1.28 (3H, t, $J=7.0$ Hz), 1.56—1.82 (3H, m), 2.13 (3H, d, $J=1.2$ Hz), 2.07—2.32 (3H, m), 2.62 (2H, t, $J=5.9$ Hz), 2.74—2.85 (2H, m), 3.53 (2H, t, $J=5.9$ Hz), 4.15 (2H, q, $J=7.0$ Hz), 4.16 (2H, q, $J=7.0$ Hz), 5.32 (1H, s), 5.82 (1H, d, $J=1.2$ Hz), 6.95—7.05 (4H, m), 7.22—7.31 (4H, m). MS m/z: 515 (M^+), 282.

1i: Yield: 88%. IR ($CHCl_3$) cm^{-1}: 2830, 1710, 1510. ^1H-NMR (90 MHz, $CDCl_3$) δ: 1.05 (3H, s), 1.28 (3H, t, $J=7.2$ Hz), 1.20—1.91 (4H, m), 2.32—2.61 (4H, m), 2.64 (2H, t, $J=6.0$ Hz), 3.55 (2H, t, $J=6.0$ Hz), 4.20 (2H, q, $J=7.2$ Hz), 5.33 (1H, s), 5.77 (1H, d, $J=16.2$ Hz), 6.82—7.13 (5H, m), 7.14—7.48 (4H, m). MS m/z: 442 ($M^+ + 1$), 210.

1j: Yield: 76%. IR ($CHCl_3$) cm^{-1}: 2950, 1710, 1610, 1515. ^1H-NMR (270 MHz, $CDCl_3$) δ: 1.29 (3H, t, $J=7.1$ Hz), 1.54—1.79 (4H, m), 2.17—2.32 (2H, m), 2.63 (2H, t, $J=5.9$ Hz), 2.68 (2H, s), 2.58—2.74 (2H, m), 3.52 (2H, t, $J=5.9$ Hz), 4.20 (2H, q, $J=7.1$ Hz), 5.30 (1H, s), 5.57 (1H, d, $J=16.1$ Hz), 6.78 (1H, d, $J=16.1$ Hz), 6.94—7.06 (6H, m), 7.17—7.34 (7H, m). MS m/z: 520 ($M^+ + 1$), 286.

1k: Yield: 72%. IR ($CHCl_3$) cm^{-1}: 2950, 1710, 1605, 1510. ^1H-NMR (90 MHz, $CDCl_3$) δ: 1.24 (3H, t, J=7.0 Hz), 1.98—2.33 (4H, m), 2.42—2.79 (6H, m), 3.52 (2H, t, J=6.1 Hz), 4.15 (2H, q, J=7.0 Hz), 5.31 (1H, s), 5.65 (1H, d, J=16.4 Hz), 6.83—7.54 (14H, m). MS m/z: 506 (M^++1), 272.

Ethyl 1-[2-Bis(4-fluorophenyl)methoxyethyl]-α-carbethoxy-4-piperidineacrylate (1c) A mixture of **4a** (1.26 g, 3.51 mmol), diethyl malonate (730 mg, 4.56 mmol), AcOH (42 mg), and piperidine (30 mg) in benzene (10 ml) was refluxed for 1.5 h, equipped with a water separator. After cooling, the reaction mixture was washed with H_2O, saturated aqueous $NaHCO_3$ solution, and brine. The residue obtained from the extracts was chromatographed on silica gel (AcOEt–hexane, 1 : 1) to give **1c** (1.57 g, 89%) as an oil. IR ($CHCl_3$) cm^{-1}: 2945, 1725, 1605. ^1H-NMR (270 MHz, $CDCl_3$) δ: 1.29 (3H, t, J=7.1 Hz), 1.32 (3H, t, J=7.1 Hz), 1.41—1.59 (2H, m), 1.64—1.76 (2H, m), 2.07 (2H, dt, J=11.7, 2.4 Hz), 2.30—2.47 (1H, m), 2.64 (2H, t, J=6.1 Hz), 2.86—2.96 (2H, m), 3.55 (2H, t, J=6.1 Hz), 4.23 (2H, q, J=7.1 Hz), 4.30 (2H, q, J=7.1 Hz), 5.33 (1H, s), 6.79 (1H, d, J=10.3 Hz), 6.96—7.05 (4H, m), 7.24—7.36 (4H, m). MS m/z: 502 (M^++1), 268.

Ethyl 1-[2-Bis(4-fluorophenyl)methoxyethyl]-α-cyano-4-piperidineacrylate (1d) Following a procedure similar to that described for **1c**, compound **1d** was obtained as an oil by treatment of **4a** with ethyl cyanoacetate. IR ($CHCl_3$) cm^{-1}: 2945, 2220, 1730, 1625, 1510. ^1H-NMR (270 MHz, $CDCl_3$) δ: 1.36 (3H, t, J=7.3 Hz), 1.48—1.78 (4H, m), 2.16 (2H, br t, J=10.7 Hz), 2.59—2.76 (1H, m), 2.67 (2H, t, J=5.9 Hz), 2.88—3.01 (2H, m), 3.56 (2H, t, J=5.9 Hz), 4.31 (2H, q, J=7.3 Hz), 5.33 (1H, s), 6.97—7.05 (4H, m), 7.24—7.31 (4H, m), 7.46 (1H, d, J=10.3 Hz). MS m/z: 455 (M^++1), 221.

Ethyl 1-[2-Bis(4-fluorophenyl)methoxyethyl]-4-(1-hydroxyethyl)-4-piperidinecarboxylate (7e) A solution of **5** (3.01 g, 7.46 mmol) in *N,N,N',N'*-tetramethylethylenediamine (7 ml) was added dropwise to a stirred solution of LDA [prepared from 1.6 M *n*-BuLi in hexane (14.0 ml, 22.4 mmol) and diisopropylamine (2.28 g, 22.5 mmol)] in anhydrous THF (20 ml) at −78 °C during 15 min under an N_2 atmosphere. The reaction mixture was stirred for 30 min at the same temperature, then a solution of acetaldehyde (1.00 g, 22.7 mmol) in anhydrous THF (10 ml) was slowly added over 10 min. The whole was stirred for 15 min at the same temperature. The reaction was quenched with saturated aqueous NH_4Cl solution, then the mixture was poured into brine, and extracted with AcOEt. The residue obtained from the AcOEt extracts was purified by column chromatography on silica gel (AcOEt) to give **7e** (2.41 g, 72%) as an oil. *Anal.* Calcd for $C_{25}H_{31}F_2NO_4$: C, 67.10; H, 6.98; N, 3.13; F, 8.49. Found: C, 67.31; H, 7.13; N, 3.10; F, 8.52. IR ($CHCl_3$) cm^{-1}: 2945, 1720, 1610, 1510. ^1H-NMR (270 MHz, $CDCl_3$) δ: 1.13 (3H, d, J=6.8 Hz), 1.29 (3H, t, J=7.0 Hz), 1.49 (1H, td, J=12.6, 4.2 Hz), 1.65 (1H, td, J=12.7, 3.6 Hz), 1.96—2.29 (5H, m), 2.62 (2H, d, J=6.1 Hz), 2.76—2.90 (2H, m), 3.55 (2H, t, J=6.1 Hz), 3.58—3.70 (1H, br), 4.22 (2H, q, J=7.0 Hz), 5.32 (1H, s), 6.94—7.05 (4H, m), 7.21—7.32 (4H, m). MS m/z: 447 (M^+), 214.

Ethyl 1-[2-Bis(4-fluorophenyl)methoxyethyl]-4-(3,7-dimethyl-1-hydroxy-6-octenyl)-4-piperidinecarboxylate (7f) Following a procedure similar to that described for **7e**, **7f** was obtained as an oil in 78% yield by treatment of **5** with citronellal. *Anal.* Calcd for $C_{33}H_{45}F_2NO_4$: C, 71.07; H, 8.13; N, 2.51; F, 6.81. Found: C, 71.29; H, 8.01; N, 2.68; F, 6.78. IR ($CHCl_3$) cm^{-1}: 2945, 1710, 1610, 1510. ^1H-NMR (270 MHz, $CDCl_3$) δ: 0.86 and 0.92 (3H, each d, J=6.6 Hz), 0.98—1.12 (1H, m), 1.14—1.33 (2H, m), 1.28 (3H, t, J=7.2 Hz), 1.33—1.58 (2H, m), 1.59 and 1.67 (each 3H, s), 1.58—1.75 (2H, m), 1.85—2.10 (5H, m), 2.13—2.27 (2H, m), 2.61 (2H, t, J=6.0 Hz), 2.74—2.87 (2H, m), 3.44—3.58 (1H, m), 3.54 (2H, t, J=6.0 Hz), 4.20 (2H, q, J=7.2 Hz), 5.04—5.13 (1H, m), 5.32 (1H, s), 6.94—7.06 (4H, m), 7.21—7.33 (4H, m). MS m/z: 557 (M^+), 324.

Ethyl 4-Acetyl-1-[2-bis(4-fluorophenyl)methoxyethyl]-4-piperidinecarboxylate (8e) A solution of DMSO (2.10 g, 26.9 mmol) in anhydrous CH_2Cl_2 (5 ml) was added dropwise to a stirred solution of oxalyl chloride (1.73 g, 13.6 mmol) in anhydrous CH_2Cl_2 (20 ml) at −78 °C over a period of 10 min under an N_2 atmosphere. The reactoin mixture was stirred for 15 min at the same temperature, then a solution of **7e** (2.41 g, 5.39 mmol) in anhydrous CH_2Cl_2 (10 ml) was added dropwise at the same temperature over a period of 15 min. Stirring was continued for an additional 15 min at the same temperature, then Et_3N (3.28 g, 32.4 mmol) was added and the whole was warmed to room temperature. The reaction was quenched with H_2O and the mixture was extracted with CH_2Cl_2. The residue obtained from the extracts was purified by column chromatography on silica gel (AcOEt–hexane, 3 : 1) to give **8e** (1.77 g, 74%) as an oil. *Anal.* Calcd for $C_{25}H_{29}F_2NO_4$: C, 67.40; H, 6.56; N, 3.14; F, 8.53. Found: C, 67.51; H, 6.75; N, 3.18; F, 8.61. IR ($CHCl_3$) cm^{-1}: 1730, 1710, 1605, 1510. ^1H-NMR (270 MHz, $CDCl_3$) δ: 1.26 (3H, t, J=7.0 Hz), 1.92—2.04 (2H, m), 2.09—2.25 (2H, m), 2.15 (3H, s), 2.30—2.41 (2H, m), 2.56—2.67 (2H, m), 2.62 (2H, d, J=6.0 Hz), 3.53 (2H, t, J=6.0 Hz), 4.20 (2H, q, J=7.0 Hz), 5.31 (1H, s), 6.97—7.03 (4H, m), 7.23—7.29 (4H, m). MS m/z: 446 (M^++1), 212.

Ethyl 1-[2-Bis(4-fluorophenyl)methoxyethyl]-4-(3,7-dimethyl-6-octenoyl)-4-piperidinecarboxylate (8f) Following a procedure similar to that described for **8e**, **8f** was obtained as an oil in 88% yield by treatment of **7f**. *Anal.* Calcd for $C_{33}H_{43}F_2NO_4$: C, 71.33; H, 7.80; N, 2.52; F, 6.84. Found: C, 71.09; H, 7.72; N, 2.48; F, 6.50. IR ($CHCl_3$) cm^{-1}: 2930, 1730, 1710, 1605, 1510. ^1H-NMR (270 MHz, $CDCl_3$) δ: 0.84 (3H, d, J=6.4 Hz), 1.05—1.37 (2H, m), 1.24 (3H, t, J=7.1 Hz), 1.58 (3H, s), 1.67 (3H, d, J=1.0 Hz), 1.88—2.13 (5H, m), 2.13—2.46 (6H, m), 2.58—2.71 (2H, m), 2.60 (2H, t, J=6.0 Hz), 3.53 (2H, t, J=6.0 Hz), 4.18 (2H, q, J=7.1 Hz), 5.03—5.12 (1H, m), 5.31 (1H, s), 6.95—7.04 (4H, m), 7.22—7.29 (4H, m). MS m/z: 510, 324.

4-Acetyl-1-[2-bis(4-fluorophenyl)methoxyethyl]piperidine (9e) A mixture of **8e** (1.031 g, 2.31 mmol), LiCl (196 mg, 4.62 mmol), and H_2O (43 mg, 2.39 mmol) in DMSO (4 ml) was refluxed for 1 h. After evaporation of the solvent, H_2O was added to the residue and the mixture was extracted with AcOEt. The residue obtained from the extracts was chromatographed on silica gel (AcOEt–hexane, 9 : 1) to give **9e** (343 mg, 40%) as an oil. *Anal.* Calcd for $C_{22}H_{25}F_2NO_2$: C, 70.76; H, 6.75; N, 3.75; F, 10.17. Found: C, 70.60; H, 6.75; N, 3.71; F, 10.18. IR ($CHCl_3$) cm^{-1}: 2945, 1705, 1605, 1510. ^1H-NMR (270 MHz, $CDCl_3$) δ: 1.56—1.74 (2H, m), 1.79—1.88 (2H, m), 2.05—2.16 (2H, m), 2.14 (3H, s), 2.18—2.30 (1H, m), 2.64 (2H, t, J=6.0 Hz), 2.88—2.98 (2H, m), 3.55 (2H, t, J=6.0 Hz), 5.33 (1H, s), 6.95—7.05 (4H, m), 7.24—7.33 (4H, m). MS m/z: 373 (M^+), 140.

1-[2-Bis(4-fluorophenyl)methoxyethyl]-4-(3,7-dimethyl-6-octenoyl)piperidine (9f) Following a procedure similar to that described for **9e**, **9f** was obtained as an oil in 73% yield by decarboxylation of **8f**. *Anal.* Calcd for $C_{30}H_{39}F_2NO_2$: C, 74.50; H, 8.13; N, 2.90; F, 7.86. Found: C, 74.68; H, 8.06; N, 2.85; F, 7.76. IR ($CHCl_3$) cm^{-1}: 2940, 1705, 1610, 1510. ^1H-NMR (270 MHz, $CDCl_3$) δ: 0.87 (3H, d, J=6.4 Hz), 1.11—1.36 (2H, m), 1.56 (3H, s), 1.67 (3H, d, J=1.0 Hz), 1.55—1.84 (4H, m), 1.89—2.16 (5H, m), 2.19—2.32 (2H, m), 2.40 (1H, dd, J=16.3, 5.6 Hz), 2.64 (2H, t, J=6.0 Hz), 2.84—2.99 (2H, m), 3.53 (2H, t, J=6.0 Hz), 5.03—5.12 (1H, m), 5.34 (1H, s), 6.95—7.05 (4H, m), 7.21—7.31 (4H, m). MS m/z: 484 (M^++1), 250.

4-Benzoyl-1-[2-bis(4-fluorophenyl)methoxyethyl]piperidine (9g) Following a procedure similar to that described for **5**, **9g** was obtained as an oil in quantitative yield by treatment of **2** with 4-benzoylpiperidine. *Anal.* Calcd for $C_{27}H_{27}F_2NO_2$: C, 74.46; H, 6.25; N, 3.22; F, 8.72. Found: C, 74.69; H, 6.39; N, 3.19; F, 8.58. IR ($CHCl_3$) cm^{-1}: 2930, 1675, 1600, 1500. ^1H-NMR (270 MHz, $CDCl_3$) δ: 1.74—1.96 (4H, m), 2.16—2.36 (2H, m), 2.72 (2H, t, J=5.9 Hz), 2.97—3.09 (2H, m), 3.19—3.33 (2H, m), 3.60 (2H, t, J=5.9 Hz), 5.36 (1H, s), 6.95—7.07 (4H, m), 7.23—7.34 (4H, m), 7.43—7.62 (3H, m), 7.88—7.97 (2H, m). MS m/z: 435 (M^+), 202.

1-[2-Bis(4-fluorophenyl)methoxyethyl]-4-cyano-4-methylpiperidine (6i) and 4-Benzyl-1-[2-bis(4-fluorophenyl)methoxyethyl]-4-cyanopiperidine (6j) Following a procedure similar to that described for **7e**, **6i** and **6j** were each obtained as oils in 80% and 79% yields by treatment of **6a** with LDA, followed by MeI and benzyl bromide, respectively.

6i: *Anal.* Calcd for $C_{22}H_{24}F_2N_2O$: C, 71.33; H, 6.53; N, 7.56; F, 10.26. Found: C, 71.59; H, 6.75; N, 7.30; F, 10.18. IR ($CHCl_3$) cm^{-1}: 2940, 1605, 1505. ^1H-NMR (90 MHz, $CDCl_3$) δ: 1.36 (3H, s), 1.23—1.60 (2H, m), 1.64—1.92 (2H, m), 2.18—3.10 (4H, m), 2.70 (2H, t, J=5.8 Hz), 3.56 (2H, t, J=5.8 Hz), 5.33 (1H, s), 6.87—7.12 (4H, m), 7.13—7.54 (4H, m). MS m/z: 370 (M^+), 137.

6j: *Anal.* Calcd for $C_{28}H_{28}F_2N_2O$: C, 75.31; H, 6.32; N, 6.27; F, 8.51. Found: C, 75.61; H, 6.52; N, 6.21; F, 8.40. IR ($CHCl_3$) cm^{-1}: 2950 (sh), 2945, 2230, 1730, 1610, 1510. ^1H-NMR (270 MHz, $CDCl_3$) δ: 1.54—1.69 (2H, m), 1.78—1.89 (2H, m), 2.40 (2H, dt, J=12.2, 2.4 Hz), 2.70 (2H, t, J=5.9 Hz), 2.85 (2H, s), 2.82—2.95 (2H, m), 3.55 (2H, t, J=5.9 Hz), 5.30 (1H, s), 6.94—7.06 (4H, m), 7.21—7.39 (9H, m). MS m/z: 447 (M^++1), 213.

1-[2-Bis(4-fluorophenyl)methoxyethyl]-4-methyl-4-piperidinecarbaldehyde (4i) and 4-Benzyl-1-[2-bis(4-fluorophenyl)methoxyethyl]-4-piperidinecarbaldehyde (4j) Following a procedure similar to that described for **4a**, **4i** and **4j** were each obtained as oils in 23% and 42% yields by treatment of **6i** and **6j** with DIBAL, respectively.

4i: IR ($CHCl_3$) cm^{-1}: 2925, 1720, 1605, 1510. ^1H-NMR (90 MHz, $CDCl_3$) δ: 1.00 (3H, s), 1.16—2.78 (8H, m), 2.61 (2H, t, J=6.0 Hz), 3.53 (2H, d, J=6.0 Hz), 5.32 (1H, s), 6.82—7.47 (8H, m), 9.50 (1H, s). MS m/z: 374 (M^++1), 140.

4j: IR ($CHCl_3$) cm^{-1}: 2945, 1730, 1610, 1510. ^1H-NMR (270 MHz,

$CDCl_3$) δ: 1.55—1.71 (2H, m), 1.91—2.02 (2H, m), 2.11 (2H, dt, J=11.6, 2.1 Hz), 2.60 (2H, t, J=6.1 Hz), 2.69—2.79 (2H, m), 2.75 (2H, s), 3.51 (2H, d, J=6.1 Hz), 5.29 (1H, s), 6.93—7.06 (6H, m), 7.19—7.36 (7H, m), 9.52 (1H, s). MS m/z: 450 (M^++1), 216.

1-[2-Bis(4-fluorophenyl)methoxyethyl]-4-phenyl-4-piperidinecarbaldehyde (4k) A mixture of **2** (2.39 g, 8.45 mmol), 4-cyano-4-phenylpiperidine hydrochloride (2.09 g, 9.38 mmol), Na_2CO_3 (4.48 g, 42.3 mmol), and a catalytic amount of NaI (90 mg) in DMF (30 ml) was warmed to 130 °C (oil bath temperature) for 4 h and then concentrated *in vacuo*. The residue was poured into H_2O and the mixture was extracted with AcOEt. The extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting residue was chromatographed on silica gel (AcOEt–hexane, 1:2) to give **6k** (3.00 g, 82%) as an oil. A 1 M DIBAL solution in hexane (10.5 ml, 10.5 mmol) was added dropwise to a stirred solution of **6k** (3.00 g, 6.94 mmol) in anhydrous THF (40 ml) at −15 °C over a period of 15 min under an N_2 atmosphere. After being stirred for 15 h at room temperature, the mixture was cooled to 0 °C and the reaction was quenched with MeOH (2 ml) followed by saturated aqueous NH_4Cl solution (15 ml). The whole was stirred for an additional 1 h at room temperature. The resulting precipitate was removed by filtration through Celite and the filtrate was extracted with AcOEt. The residue obtained from the extracts was chromatographed on silica gel (AcOEt–hexane, 1:2) to afford **4k** (0.78 g, 26%) as an oil. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.81—3.00 (8H, m), 2.62 (2H, t, J=6.0 Hz), 3.55 (2H, d, J=6.0 Hz), 5.32 (1H, s), 6.83—7.52 (13H, m), 9.44 (1H, s). MS m/z: 435 (M^+), 202.

1-(2-Diphenylmethoxyethyl)-4-piperidinecarbaldehyde and 1-[2-(4-Chlorophenyl)phenylmethoxyethyl]-4-piperidinecarbaldehyde Following a procedure similar to that described for **4a**, the title compounds were each prepared as oils in 51% and 49% yields by treatment of benzhydryl 2-chloroethyl ether[4] and (4-chlorophenyl)phenylmethyl 2-chloroethyl ether[4] with 4-cyanopiperidine[5] followed by reduction with DIBAL, respectively.

1-(2-Diphenylmethoxyethyl)-4-piperidinecarbaldehyde: ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.58—1.74 (3H, m), 1.82—1.94 (2H, m), 2.15—2.28 (1H, m), 2.19 (2H, dt, J=11.1, 2.9 Hz), 2.67 (2H, d, J=5.9 Hz), 2.87 (2H, td, J=11.7, 3.9 Hz), 3.59 (2H, t, J=5.9 Hz), 5.37 (1H, s), 7.20—7.36 (10H, m), 9.63 (1H, d, J=1.5 Hz). MS m/z: 324 (M^++1), 126.

1-[2-(4-Chlorophenyl)phenylmethoxyethyl]-4-piperidinecarbaldehyde: ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.59—1.74 (2H, m), 1.82—1.95 (2H, m), 2.14—2.29 (1H, m), 2.20 (2H, dt, J=10.9, 3.1 Hz), 2.66 (2H, d, J=6.0 Hz), 2.85 (2H, td, J=11.7, 3.9 Hz), 3.57 (2H, d, J=6.0 Hz), 5.34 (1H, s), 7.22—7.35 (9H, m), 9.64 (1H, d, J=1.0 Hz). MS m/z: 358 (M^++1), 126.

Ethyl 1-(2-Diphenylmethoxyethyl)-4-piperidineacrylate (10a) and Ethyl 1-[2-(4-Chlorophenyl)phenylmethoxyethyl]-4-piperidineacrylate (10b) Following a procedure similar to that described for **1a**, **10a** and **10b** were each obtained as oils in 48% and quantitative yields by treatment of 1-(2-diphenylmethoxyethyl)-4-piperidinecarbaldehyde and 1-[2-(4-chlorophenyl)phenylmethoxyethyl]-4-piperidinecarbaldehyde with triethyl phosphonoacetate, respectively.

10a: IR ($CHCl_3$) cm^{-1}: 2930, 1710, 1650, 1450. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.28 (3H, t, J=7.2 Hz), 1.40—1.58 (2H, m), 1.66—1.76 (2H, m), 2.05—2.20 (1H, m), 2.09 (2H, dt, J=11.7, 2.4 Hz), 2.67 (2H, t, J=6.1 Hz), 2.88—3.00 (2H, m), 3.59 (2H, t, J=6.1 Hz), 4.18 (2H, q, J=7.2 Hz), 5.37 (1H, s), 5.77 (1H, dd, J=15.7, 1.2 Hz), 6.91 (1H, dd, J=15.7 Hz, 6.8 Hz), 7.22—7.36 (10H, m). MS m/z: 394 (M^++1), 196.

10b: IR ($CHCl_3$) cm^{-1}: 2945, 1710, 1650, 1490. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.29 (3H, t, J=7.1 Hz), 1.39—1.55 (2H, m), 1.66—1.81 (2H, m), 2.03—2.18 (1H, m), 2.09 (2H, br t, J=10.5 Hz), 2.66 (2H, t, J=6.1 Hz), 2.89—2.98 (2H, m), 3.57 (2H, t, J=6.1 Hz), 4.18 (2H, q, J=7.1 Hz), 5.34 (1H, s), 5.78 (1H, dd, J=15.8, 1.2 Hz), 6.91 (1H, dd, J=15.8, 6.8 Hz), 7.22—7.35 (9H, m). MS m/z: 428 (M^++1), 196.

Rat Passive Cutaneous Anaphylaxis (PCA) Assay Anti-ovalbumin rat serum was produced by the method of Mota.[7] SD strain male rats were immunized by an intramuscular injection of 0.4 ml of 10% ovalbumin (OA) solution and an intraperitoneal injection of 4 ml of 2×10^{10} /ml killed *Bordetella pertussis* organisms. They were then bled 15 d after this sensitization. The anti-serum was separated and kept at −70 °C. Male Std: Sprague-Dawley rats (140 g) were intradermally injected with 0.05 ml of a dilute solution of OA in one site of the shaved ventral skin. Forty-eight hours later, the PCA reaction was induced by intravenous administration of a 1% Evans-blue saline solution containing 0.8 mg of OA. The rats were sacrificed 30 min after the challenge, and the dorsal skin was removed to determine the extravasated dye at each reaction site. The dye was extracted by the method of Harada[8] and was quantified by spectrometry. Test compounds were dissolved or suspended in a 0.5% tragacanth aqueous solution and administered orally to the rats 1 h before antigen challenge. The antiallergic activity of the compounds is expressed as percent inhibition of the dye release compared with the control group.

Antigen-Induced Bronchoconstriction The anti-asthmatic effect of test compounds was examined by behavioral observation of actively sensitized guinea pigs after antigen inhalation. Male guinea pigs were sensitized with 0.5 ml of 5% OA injected subcutaneously and 0.5 ml intraperitoneally. The second booster injections were performed 7 d later. These animals were used 8 or 9 d after the last injection. PCA titer after 24 h was 256, but PCA activity after 10 d was lost. Therefore, this model is thought to be of IgG_1 type. Five animals of one group were exposed to aerosolized OA solution (10 mg/ml) for 6 min using an ultrasonic nebulizer (NE-U11B, Omron) in a plastic chamber (48 × 48 × 60 cm). Under these conditions control animals convulsed within 3 min, falling on their side with symptoms of dyspnea resulting from bronchoconstriction. Test compounds were administered orally 1 h before OA inhalation and evaluated for their ability to prevent convulsion. ED_{50} values were determined for each drug by Litchfield–Wilcoxon analysis.

Antigen-Induced Histamine Release Assay Male Sprague-Dawley rats (140 g) were injected intraperitoneally with 2 ml of a 1:4 dilution of the rat serum containing OA-specific rat IgE. Forty-eight hours later, the animals were injected intraperitoneally with 5 ml of Tyrode solution containing 0.4 mg/ml OA and 10 units/ml heparin. Five minutes later, the rats were sacrificed by exposure to carbon dioxide. The peritoneal exudate solution was collected by opening the peritoneal cavity over a funnel into polycarbonate tubes in ice. The supernatants were separated from the cellular residue by centrifuging at 150 *g* for 5 min at 4 °C. Supernatant histamine content was determined by the modified Shore's method. Test compounds were dissolved or suspended in a 0.5% tragacanth aqueous solution and administered orally to the rats 1 h before antigen challenge. The inhibition of histamine release induced by each compound is expressed as percent inhibition of the histamine content compared with the control group.

Slow-Reacting Substance of Anaphylaxis (SRS-A) Release Assay The ability of the compounds to inhibit the formation and release of SRS-A was investigated by employing the technique of Watanabe–Kohno and Parker.[9] In these experiments, albumin was used as the antigen. Actively sensitized male Hartley guinea pigs (Japan SLC, Shizuoka, Japan) weighing 350—600 g were anesthetized with $CHCl_3$ and exsanguinated *via* the abdominal aorta and inferior vena cava. The lungs and the heart were removed from the thorax. Before the lung was perfused *via* the pulmonary artery with 40 ml of cold Tyrode solution, the apex of the heart was removed to allow free flow of the perfusate. Peripheral parenchymal tissue was chopped into 2 mm^3 fragments. The fragments were then rinsed 3 times with cold medium. Four hundred mg of the fragments was suspended in Tyrode solution (3.88 ml), which had been preincubated with various concentrations of test compounds or the control buffer (0.02 ml) at 37 °C for 15 min. Afterward, antigen (final; 200 μg/ml) or a stimulator (leukotriene D_4, platelet activating factor, histamine and U-46619) solution was added (0.1 ml) and the mixture was incubated for 15 min. The reaction was stopped by dipping the container in an ice bath. The samples were then centrifuged at 600 *g* for 5 min at 4 °C and the supernatant was collected for histamine, thromboxane, prostaglandins, and leukotrienes determinations. From the results, the concentration of the test compound required to inhibit by 50% the release of SRS-A was determined.

References and Notes

1) P. J. Barnes, *J. Allergy Clin. Immunol.*, **83**, 1013 (1989).
2) *a*) A. J. Lewis, J. H. Musser, J. Chang, and P. J. Silver, *Prog. Med. Chem.*, **22**, 293 (1985); *b*) J. L. Suschitzky and P. Sheard, *ibid.*, **21**, 1 (1984); *c*) D. J. Wolanin and J. B. Campbell, *Annu. Rep. Med. Chem.*, **26**, 113 (1991).
3) H. Fukumi, T. Sakamoto, M. Sugiyama, Y. Iizuka, and T. Yamaguchi, Japan. Patent Kokai 2212472 (1990) [*Chem. Abstr.*, **114**, 42585*x* (1990)].
4) A. Buzas, *J. Med. Chem.*, **23**, 149 (1980).
5) A. A. Carr and R. A. Farr, Ger. Patent 3031929 (1981) [*Chem. Abstr.*, **95**, 42926*y* (1981)].
6) A. P. Krapcho, J. F. Weimaster, J. M. Eldridge, E. G. E. Jahngen, Jr., A. J. Lovey, and W. P. Stephens, *J. Org. Chem.*, **43**, 138 (1978).
7) I. Mota, *Immunology*, **7**, 681 (1964).
8) M. Harada, M. Takeuchi, T. Fukao, and K. Katagiri, *J. Pharm. Pharmacol.*, **23**, 218 (1971).
9) S. Watanabe-Kohno and C. W. Parker, *J. Immunol.*, **125**, 946 (1980).