Synthesis and Pharmacological Evaluation of 1-Alkyl-*N*-[(1*R*)-1-(4-fluorophenyl)-2-methylpropyl]piperidine-4-carboxamide Derivatives as Novel Antihypertensive Agents

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We synthesized and evaluated inhibitory activity against T-type Ca^{2+} channels for a series of 1-alkyl-*N*-[(1*R*)-1-(4-fluorophenyl)-2-methylpropyl]piperidine-4-carboxamide derivatives. Structure–activity relationship studies have revealed that the isopropyl substituent at the benzylic position plays an important role in exerting potent inhibitory activity, and the absolute configuration of the benzylic position was found to be opposite that of mibefradil, which was first launched as a new class of T-type Ca^{2+} channel blocker. Oral administration of *N*-[(1*R*)-1-(4-fluorophenyl)-2-methylpropyl]-1-[2-(3-methoxyphenyl)ethyl]piperidine-4-carboxamide (**17f**) lowered blood pressure in spontaneously hypertensive rats without inducing reflex tachycardia, an adverse effect often caused by traditional L-type Ca^{2+} channel blockers.

Key words antihypertensive agent; T-type Ca^{2+} channel; mibefradil; piperidine-4-carboxamide

Calcium ions are essential for life and the most common signal transduction element in cells, transmitting signals by entering cells through ion channels on the plasma membrane in response to membrane depolarization.¹⁾ Investigation into the different subtypes of voltage-dependent Ca^{2+} channels has resulted in definition of two main classes: one responding to strong depolarization known as a high-voltage-activated (HVA) Ca^{2+} channel, and another responding to weak depolarization, known as low-voltage-activated (LVA) Ca^{2+} channel. Based on results of several functional and pharmacological studies, HVA Ca^{2+} channels may be further subdivided into L-, N-, P/Q-, and R-types, with LVA Ca^{2+} channel otherwise known as T-type channels.^{2,3)} Among these subdivisions, T-type Ca^{2+} channels are believed to play an important role in initial depolarization of the sinus and atrioventricular (AV) nodes⁴⁾ and are therefore regarded as important therapeutic targets for treating various cardiovascular diseases such as hypertension, angina, heart failure, and arrhythmia.

Mibefradil (**1**) was first launched as a new class of selective T-type Ca^{2+} channel blocker.⁵⁾ This compound has different structural and pharmacological characteristics from traditional L-type Ca^{2+} channel blockers. In addition to causing vasodilation, blockade of T-type Ca^{2+} channels slows the sinus rate and prolongs AV nodal conduction without adverse negative inotropic or positive chronotropic cardiac actions.^{6,7)} However, despite its excellent antihypertensive effects, mibefradil was withdrawn from the market in 1998 due to its pharmacokinetic interactions with other drugs metabolized by cytochrome P450.^{8,9)} Since the withdrawal of mibefradil, increased interest in T-type Ca^{2+} channels as a therapeutic target has fueled significant efforts to discover novel T-type Ca^{2+} channel blockers.^{10–40)}

We recently described the synthesis and pharmacological evaluation of a novel set of T-type Ca^{2+} channel blockers and described the relationship between blockade of T-type Ca^{2+} channels and cardiovascular effects such as bradycardic activity and antihypertensive effects.^{41,42)} Compound **2** showed

potent inhibitory activity against T-type Ca^{2+} channels with an IC_{50} value of $0.089\ \mu\text{M}$ in Ca^{2+} influx assay and elicited *in vivo* antihypertensive effects in spontaneously hypertensive rats without inducing reflex tachycardia by oral administration (Fig. 1). We further optimized compound **2** in an attempt to improve its *in vivo* potency, as the antihypertensive effect of **2** was less potent than that of mibefradil. We considered that the low *in vivo* efficacy of compound **2** was caused by its high lipophilicity. Compound **2** should be slightly lipophilic ($c\log P=5.00$) to maintain its blood concentration because highly lipophilic compound is easily metabolized by P450 enzymes, in general (Lipinski's rule of five). Therefore, we designed compound **3a**, in which one methylene group of **2** was eliminated ($c\log P=4.84$), and found it to be as potent a T-type Ca^{2+} channel blocker as compound **2**. Encouraged by these data, we planned further optimization studies of compound **3a**.

Here, we describe the synthesis, structure–activity relationships, and pharmacological properties of 1-alkyl-*N*-

Fig. 1. Chemical Structures of T-Type Ca^{2+} Channel Blocker

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[(1*R*)-1-(4-fluorophenyl)-2-methylpropyl]piperidine-4-carboxamide derivatives as novel antihypertensive agents.

Synthesis The preparation of *N*-(1-ethyl-1-phenylpropyl)-1-(2-phenylethyl)piperidine-4-carboxamide derivatives is outlined in Chart 1. Dialkylation of methyl benzoates **4a–f** with ethylmagnesium bromide followed by Ritter reaction with chloroacetonitrile⁴³ afforded chloroacetamides **5a–f**, which were then subsequently converted to piperidines **6a–f** in a three-step sequence consisting of deprotection of the chloroacetyl group with thiourea, condensation with 1-*tert*-butoxycarbonyl(Boc)piperidine-4-carboxylic acid in the presence of 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (WSCD) and 1-hydroxybenzotriazole (HOBt), and deprotection of the Boc group by treatment with hydrogen chloride. Alkylation of piperidines **6a–f** was accomplished by reductive amination with phenylacetaldehyde and sodium triacetoxyborohydride to afford the final compounds **3a–f**.

Obtaining compound **3g**, which bears a 4-methoxy substituent at the benzene ring, was impossible using the method shown in Chart 1, possibly because the 4-methoxy-substituted benzylic carbocation was not reactive enough to undergo the Ritter reaction. We therefore synthesized compound **3g** as follows (Chart 2): 4-methoxyphenylacetonitrile **7** was converted to carboxylic acid **8** in a three-step sequence involving dialkylation of the benzylic position with iodo-

ethane, reduction of the nitrile group with DIBAL-H, and re-oxidation with NaClO₂. The Curtius rearrangement of carboxylic acid **8** with diphenylphosphoryl azide (DPPA) and benzyl alcohol followed by deprotection of the benzyloxycarbonyl (Cbz) group afforded the corresponding amine, which was then coupled with 1-(Boc)piperidine-4-carboxylic acid to give compound **9**. Deprotection followed by alkylation resulted in the target compound **3g**.

The compound bearing a cyclopentyl moiety at the benzylic position (**13**) was synthesized as illustrated in Chart 3. Treatment of 4-fluorophenylacetonitrile **10** with 1,4-dibromobutane and NaH followed by acid hydrolysis of the nitrile group afforded carboxylic acid **11**. Curtius rearrangement followed by deprotection of the Cbz group then produced the amine, which was subsequently treated with 1-(Cbz)piperidine-4-carbonyl chloride to provide compound **12**. Hydrogenation followed by alkylation produced compound **13**.

The synthesis of isopropyl analogues **17a–k** is depicted in Chart 4. Curtius rearrangement of optically active carboxylic acid **14**⁴⁴ followed by deprotection of the Boc group yielded amine **15**. Condensation of this amine **15** with 1-(Boc)piperidine-4-carboxylic acid and deprotection provided the key intermediate **16**. Alkylation of the piperidine **16** was carried out *via* two general methods, A and B. Compounds **17a–e**, **17h–k** were synthesized by Method A, which involved reductive amination of **16** with corresponding aldehy-

Chart 1

Chart 2

Reagents and conditions: (a) $\text{Br}(\text{CH}_2)_4\text{Br}$, NaH, DMF; (b) H_2SO_4 , H_2O ; (c) DPPA, Et_3N , BnOH, PhMe; (d) H_2 , Pd/C, AcOEt; (e) 1-(Cbz)piperidine-4-carbonyl chloride, Et_3N , CH_2Cl_2 ; (f) H_2 , Pd/C, EtOH; (g) phenylacetaldehyde, $\text{NaBH}(\text{OAc})_3$, AcOH, CH_2Cl_2 .

Chart 3

- 17a: R=H
 17b: R=2- CF_3
 17c: R=3- CF_3
 17d: R=4- CF_3
 17e: R=2-MeO
 17f: R=3-MeO
 17g: R=4-MeO
 17h: R=2,3-diMeO
 17i: R=3,4-diMeO
 17j: R=3,5-diMeO
 17k: R=2,5-diMeO

Reagents and conditions: (a) DPPA, Et_3N , *t*BuOH; (b) HCl, AcOEt; (c) 1-(Boc)piperidine-4-carboxylic acid, WSCD, HOBT, Et_3N , CH_3CN ; (d) HCl, AcOEt; (e) aldehyde, $\text{NaBH}(\text{OAc})_3$, AcONa, CH_2Cl_2 (Method A) or alkyl-OTs, K_2CO_3 , CH_3CN (Method B).

Chart 4

Reagents and conditions: (a) $\text{R}-\text{Br}$, K_2CO_3 , DMF; (b) $\text{Ph}_3\text{P}^+\text{CH}_2\text{OMeCl}^-$, *t*BuOK, THF; (c) HCO_2H ; (d) aldehyde, $\text{NaBH}(\text{OAc})_3$, AcONa, CH_2Cl_2 ; (e) LiAlH_4 , THF.

Chart 5

des, whereas compounds **17f, g** were prepared by Method B, which involved alkylation of **16** with the corresponding tosylates under basic conditions.

Compounds **17l—n** were synthesized as shown in Chart 5. Alkylation of 3-hydroxybenzaldehyde **18** with corresponding bromides followed by transformation of the benzaldehyde moiety to phenylacetaldehyde **19** by Wittig reaction and treatment with formic acid yielded compounds **19a** and **b**. Alkylation of piperidine **16** by reaction with the correspond-

ing aldehydes (**19a, b**) and sodium triacetoxyborohydride subsequently produced compounds **17l** and **m**, respectively. LiAlH_4 reduction of the ester group afforded the compound **17n**.

Results and Discussion

The inhibitory activities of the synthesized compounds against T-type Ca^{2+} channels were assessed by measuring the inhibition of Ca^{2+} influx in HEK293 cells stably expressing

human Cav3.1 ($\alpha 1G$).

We first investigated the effect of substituents on the benzene ring on the left-hand side of **3a** (Table 1). The inhibitory activity of the parent compound **3a**, with a fluorine atom at the 4-position, was found to be as potent as that of compound **2** ($IC_{50}=0.13\ \mu M$). Elimination of this fluorine reduced the inhibitory activity (**3b**), and transposition to the 2- or 3-position (**3c**, **d**) also reduced the activity compared to **3a** by 3- and 4-fold, respectively. While introduction of a methoxy group (**3e–g**) improved activity over that of the unsubstituted compound (**3b**), these substituted compounds were slightly less potent than the parent compound (**3a**) bearing a fluorine at the 4-position. Taken together, these results indicated that the introduction of a fluorine atom at the 4-position on the benzene ring of **3b** is optimal for conferring potent T-type Ca^{2+} channel inhibitory activity.

We then evaluated the compounds with several substituents at the benzylic position of **3a** (Table 2). Inhibitory activity of the cyclopentyl derivative (**13**) was reduced by 2-

Table 1. T-Type Ca^{2+} Channel-Blocking Activity of 1-(2-Phenylethyl)-*N*-(3-phenylpentan-3-yl)piperidine-4-carboxamide Derivatives (**3a–g**)

Compound	Structure	$IC_{50}\ (\mu M)^a$
3a	R=4-F	0.13
3b	R=H	0.55
3c	R=3-F	0.53
3d	R=2-F	0.39
3g	R=4-OMe	0.26
3e	R=3-OMe	0.26
3f	R=2-OMe	0.33

^a) Inhibition of Ca^{2+} influx through T-type Ca^{2+} channels. See Experimental.

Table 2. T-Type Ca^{2+} Channel-Blocking Activity of 1-(2-Phenylethyl)-piperidine-4-carboxamide Derivatives (**3a**, **13**, *ent*-**17a**, **17a**)

Compound	R	$IC_{50}\ (\mu M)^a$
3a		0.13
13		0.30
<i>ent</i> - 17a		0.73
17a		0.15

^a) Inhibition of Ca^{2+} influx through T-type Ca^{2+} channels. See Experimental.

fold compared to **3a**. To reduce the lipophilicity of these compounds, an isopropyl group was introduced instead of the diethyl group. We initially evaluated the *S*-configured compound (*ent*-**17a**), which shared same absolute configuration as mibefradil, and surprisingly found it to be less potent than **3a**. In contrast, the *R*-configured compound (**17a**) had similar inhibitory activity to **3a** ($IC_{50}=0.15\ \mu M$). These results revealed that the stereochemistry of the substituent at the benzylic position strongly influences the inhibitory activity against T-type Ca^{2+} channels and that the more potent compound had an *R* configuration, opposite that of mibefradil.

Finally, we modified the pendant benzene ring of **17a** of the phenethyl side chain (Table 3). The introduction of trifluoromethyl groups reduced activity compared to the unsubstituted compound (**17b–d**). Further, while introduction of methoxy groups at the 2- and 4-positions retained the inhibitory activity (**17e,g**), 3-methoxy substitution increased the activity. Indeed, the 3-methoxy derivative (**17f**) was the most potent in our series with an IC_{50} value of $0.076\ \mu M$. These results indicated that the introduction of an electron-donating substituent was effective in enhancing the T-type Ca^{2+} channel blocking ability. We further explored electron-donating substitution on the phenyl ring and found that conversion of the methoxy group to ethoxycarbonylmethoxy (**17l**), 2-methoxyethoxy (**17m**), or hydroxyethoxy (**17n**) groups decreased the activity compared to **17f**, respectively. While additional substituents were introduced to enhance the inhibitory activity of **17f**, introduction of another methoxy group resulted in a decrease in activity compared to **17f** (**17h–k**). These results revealed that the ability to inhibit T-type Ca^{2+} channels is sensitive to the bulkiness of the substituents on the pendant benzene ring and that the introduction of an additional substituent to **17f** had a negligible influence on inhibitory activity.

Based on the findings described above, we selected compound **17f** for the evaluation of the bradycardic activity in isolated guinea pig right atria (Table 4). Compound **17f** was

Table 3. T-Type Ca^{2+} Channel-Blocking Activity of *N*-[(1*R*)-1-(4-Fluorophenyl)-2-methylpropyl]-1-(2-phenylethyl)piperidine-4-carboxamide Derivatives (**17a–n**)

Compound	Structure	$IC_{50}\ (\mu M)^a$
17a	R=H	0.15
17b	R=2-CF ₃	0.21
17c	R=3-CF ₃	0.16
17d	R=4-CF ₃	0.26
17e	R=2-OMe	0.11
17f	R=3-OMe	0.076
17g	R=4-OMe	0.13
17l	R=3-OCH ₂ CO ₂ Et	0.13
17m	R=3-OCH ₂ CH ₂ OMe	0.15
17n	R=3-OCH ₂ CH ₂ OH	0.42
17h	R=2,3-diOMe	0.13
17i	R=3,4-diOMe	0.12
17j	R=3,5-diOMe	0.13
17k	R=2,5-diOMe	0.21

^a) Inhibition of Ca^{2+} influx through T-type Ca^{2+} channels. See Experimental.

Table 4. Pharmacological Properties of Selected Compounds (**17f**, **1**)

Compound	T-Type ^{a)} IC ₅₀ (μM)	Bradycardic activity ^{b)} EC ₃₀ (μM)
17f	0.076	2.1
Mibefradil (1)	0.20	2.9

a) Inhibition of Ca²⁺ influx through T-type Ca²⁺ channels. See Experimental. b) Concentration required to elicit a 30% reduction in spontaneous beat rates from baseline in isolated guinea pig right atria. See Experimental.

Fig. 2. Effects of **17f** and Mibefradil (**1**) on Mean Blood Pressure (MBP) and Heart Rate (HR) in Conscious Spontaneously Hypertensive Rats

The compounds were orally administered at 0 h. The values are means $\pm$ standard error of the mean from at least three experiments.

found to exert potent bradycardic activity, with an EC₃₀ value of 2.1 μM, a value of comparable to that of mibefradil (EC₃₀=2.9 μM).

Given its potent inhibitory activity against T-type Ca²⁺ channels and the bradycardic activity displayed in isolated guinea pig right atria, **17f** was submitted for further pharmacological evaluations. Mibefradil and **17f** were orally administered to spontaneously hypertensive rats and the effects on mean blood pressure (MBP) and heart rate (HR) were examined (Fig. 2). Compound **17f** significantly reduced MBP, with efficacy sustained for at least 8 h. In addition, no reflex tachycardia was observed despite the potent antihypertensive activity of the compounds. The magnitude and duration of reduction in blood pressure effected by **17f** were not only more potent than compound **2** by 3-fold, but also equipotent to those induced by mibefradil. Given these findings, we hypothesize that this enhanced *in vivo* efficacy of **17f** is due to the compound's improved pharmacokinetic profile in spontaneously hypertensive rats.

Conclusion

A series of 1-alkyl-N-[(1*R*)-1-(4-fluorophenyl)-2-methylpropyl]piperidine-4-carboxamide were synthesized and evaluated. Structure-activity relationship studies of this novel class of compounds revealed that the isopropyl substituent at the benzylic position plays an important role in imbuing po-

tent inhibitory activity against T-type Ca²⁺ channels and that the absolute configuration of the benzylic asymmetric center was opposite that of mibefradil. We also found that 4-fluoro substitution on the phenyl ring of the benzyl moiety and 3-methoxy substitution on the phenyl ring in the phenethyl moiety optimally improved T-type Ca²⁺ channel blocking activity. Of this series, N-[(1*R*)-1-(4-fluorophenyl)-2-methylpropyl]-1-[2-(3-methoxyphenyl)ethyl]piperidine-4-carboxamide (**17f**) exerted an antihypertensive effect without undesirable reflex tachycardia on oral administration to spontaneously hypertensive rats. Further, the magnitude and duration of the reduction in blood pressure effected by the compound (**17f**) were equipotent to those induced by mibefradil. Further research to identify novel antihypertensive agents superior in efficacy to currently available agents is underway and will be reported in due course.

Experimental

¹H-NMR spectra were obtained on a JEOL JNM-EX400 spectrometer and the chemical shifts are expressed in δ (ppm) values with tetramethylsilane as an internal standard. Abbreviations of ¹H-NMR signal patterns are as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; m, multiplet; br, broad. Mass spectra were obtained on a JEOL JMS-DX300 or HITACHI M-80 spectrometer. Column chromatography on silica gel was performed with Kieselgel 60 (E. Merck).

2-Chloro-N-[3-(4-fluorophenyl)pentan-3-yl]acetamide (5a) To a solution of methyl 4-fluorobenzoate (**4a**, 10.0 g, 59.5 mmol) in tetrahydrofuran (THF) (50 ml) was added portionwise ethylmagnesium bromide (3.0 M in Et₂O; 65 ml, 195 mmol) at -20 °C and the mixture was gradually warmed to 0 °C for 2 h. The mixture was poured onto ice-cooled aqueous ammonium chloride solution and then extracted with AcOEt. The organic layer was washed with brine, dried over Na₂SO₄, and evaporated *in vacuo* to give 3-(4-fluorophenyl)pentan-3-ol (11.2 g, 59.5 mmol) as a colorless oil, which was used for the next step without further purification. To an ice-cooled solution of the alcohol obtained above (11.2 g, 59.5 mmol) and chloroacetonitrile (10 ml, 159 mmol) in AcOH (30 ml) was added slowly sulfuric acid (12 ml, 225 mmol) and the mixture was stirred at room temperature for 4 h. The mixture was poured onto ice-water and the resulting precipitate was collected by filtration to give the title compound **5a** (13.8 g, 2 steps 90%) as a colorless solid. ¹H-NMR (CDCl₃) δ: 0.75 (6H, t, *J*=7.6 Hz), 2.00–2.21 (4H, m), 4.02 (2H, s), 6.69 (1H, s), 7.03 (2H, dd, *J*=8.4, 8.8 Hz), 7.26 (2H, dd, *J*=4.8, 8.8 Hz). MS (FAB) *m/z*: 256 (M⁺-1).

2-Chloro-N-[3-(phenyl)pentan-3-yl]acetamide (5b) The title compound was prepared in the same manner as described for **5a** using **4b** instead of **4a**, in 80% yield. ¹H-NMR (CDCl₃) δ: 0.74 (6H, t, *J*=7.2 Hz), 2.15 (4H, q, *J*=7.2 Hz), 4.04 (2H, s), 6.74 (1H, s), 7.23–7.38 (5H, m). MS (FAB) *m/z*: 240 (M⁺+1).

2-Chloro-N-[3-(3-fluorophenyl)pentan-3-yl]acetamide (5c) The title compound was prepared in the same manner as described for **5a** using **4c** instead of **4a**, in 34% yield. ¹H-NMR (CDCl₃) δ: 0.76 (6H, t, *J*=7.6 Hz), 2.00–2.25 (4H, m), 4.03 (2H, s), 6.70 (1H, s), 6.92–7.09 (3H, m), 7.26–7.34 (1H, m). MS (FAB) *m/z*: 256 (M⁺-1).

2-Chloro-N-[3-(2-fluorophenyl)pentan-3-yl]acetamide (5d) The title compound was prepared in the same manner as described for **5a** using **4d** instead of **4a**, in 73% yield. ¹H-NMR (CDCl₃) δ: 0.77 (6H, t, *J*=7.6 Hz), 2.10–2.34 (4H, m), 4.00 (2H, s), 6.80 (1H, s), 6.97–7.05 (1H, m), 7.09–7.15 (1H, m), 7.20–7.32 (2H, m). MS (FAB) *m/z*: 256 (M⁺-1).

2-Chloro-N-[3-(3-methoxyphenyl)pentan-3-yl]acetamide (5e) The title compound was prepared in the same manner as described for **5a** using **4e** instead of **4a**, in 67% yield. ¹H-NMR (CDCl₃) δ: 0.74 (6H, t, *J*=7.6 Hz), 2.13 (4H, q, *J*=7.6 Hz), 3.97 (3H, s), 4.06 (2H, s), 6.73 (1H, s), 6.74–6.90 (3H, m), 7.25–7.29 (1H, m). MS (FAB) *m/z*: 270 (M⁺+1).

2-Chloro-N-[3-(2-methoxyphenyl)pentan-3-yl]acetamide (5f) The title compound was prepared in the same manner as described for **5a** using **4f** instead of **4a**, in 36% yield. ¹H-NMR (CDCl₃) δ: 0.72 (6H, t, *J*=7.6 Hz), 2.05–2.20 (2H, m), 2.34–2.44 (2H, m), 3.85 (3H, s), 3.98 (2H, s), 6.90–6.99 (2H, m), 7.15–7.33 (2H, m), 7.77 (1H, s). MS (FAB) *m/z*: 270 (M⁺+1).

N-[3-(4-Fluorophenyl)pentan-3-yl]piperidine-4-carboxamide Hydrochloride (6a) To a solution of **5a** (1.0 g, 3.88 mmol) and AcOH

(1.0 ml) in EtOH (10 ml) was added thiourea (0.40 g, 5.25 mmol) and the mixture was refluxed for 16 h. After the mixture was cooled to room temperature, resulting precipitate was removed by filtration and the filtrate was concentrated *in vacuo*. The resulting residue was partitioned between aqueous potassium carbonate solution and AcOEt. The organic layer was washed with brine, dried over Na_2SO_4 , and evaporated *in vacuo* to give 3-(4-fluorophenyl)pentan-3-amine (0.77 g) as a colorless oil, which was used for the next step without further purification. To an ice-cooled mixture of the amine obtained above (0.77 g), 1-(Boc)piperidine-4-carboxylic acid (0.95 g, 4.14 mmol), and HOBt (0.55 g, 4.07 mmol) in CH_3CN (10 ml) was added WSCD (0.80 g, 4.18 mmol) and the mixture was stirred at room temperature for 3 d. The reaction mixture was concentrated *in vacuo* and partitioned between H_2O and AcOEt. The organic layer was washed successively with 5% aqueous citric acid solution, saturated aqueous sodium bicarbonate solution, and brine, dried over Na_2SO_4 , and evaporated *in vacuo*. The resulting residue was purified by column chromatography on silica gel (AcOEt/hexane=1/2) to give *tert*-butyl 4-([3-(4-fluorophenyl)pentan-3-yl]carbamoyl)piperidine-1-carboxylate (1.10 g, 2 steps 72%) as a colorless solid. To an ice-cooled solution of the *N*-Boc derivative obtained above (1.10 g, 2.80 mmol) in AcOEt (10 ml) was added 4 M HCl–AcOEt (5.0 ml, 20.0 mmol) and the mixture was stirred at room temperature for 2 h. After concentration of the reaction mixture, the resulting solid was suspended with AcOEt and collected by filtration to give the title compound **6a** (0.93 g, quantitative) as a light yellow solid. $^1\text{H-NMR}$ (DMSO- d_6) δ : 0.62 (6H, t, $J=7.6$ Hz), 1.59–1.75 (2H, m), 1.77–1.92 (4H, m), 1.98–2.10 (2H, m), 2.50–2.62 (1H, m), 2.73–2.92 (2H, m), 3.22–3.38 (2H, m), 7.08 (2H, dd, $J=8.4$, 8.8 Hz), 7.26 (2H, dd, $J=4.8$, 8.8 Hz), 7.78 (1H, s), 8.43 (1H, br s), 8.78 (1H, br s). MS (FAB) m/z : 293 ($\text{M}^+ + 1$).

***N*-(3-Phenylpentan-3-yl)piperidine-4-carboxamide Hydrochloride (6b)** The title compound was prepared in the same manner as described for **6a** using **5b** instead of **5a**, in 64% yield. $^1\text{H-NMR}$ (DMSO- d_6) δ : 0.62 (6H, t, $J=7.6$ Hz), 1.59–1.75 (2H, m), 1.77–1.90 (4H, m), 1.99–2.10 (2H, m), 2.55–2.64 (1H, m), 2.75–2.90 (2H, m), 3.22–3.38 (2H, m), 7.10–7.20 (1H, m), 7.20–7.30 (4H, m), 7.75 (1H, s), 8.57 (1H, br s), 9.02 (1H, br s). MS (FAB) m/z : 275 ($\text{M}^+ + 1$).

***N*-[3-(3-Fluorophenyl)pentan-3-yl]piperidine-4-carboxamide Hydrochloride (6c)** The title compound was prepared in the same manner as described for **6a** using **5c** instead of **5a**, in 63% yield. $^1\text{H-NMR}$ (DMSO- d_6) δ : 0.63 (6H, t, $J=7.6$ Hz), 1.60–1.75 (2H, m), 1.76–1.90 (4H, m), 1.98–2.10 (2H, m), 2.55–2.64 (1H, m), 2.75–2.90 (2H, m), 3.22–3.35 (2H, m), 6.96–7.03 (2H, m), 7.08 (1H, d, $J=7.2$ Hz), 7.28–7.34 (1H, m), 7.84 (1H, s), 8.56 (1H, br s), 9.01 (1H, br s). MS (FAB) m/z : 293 ($\text{M}^+ + 1$).

***N*-[3-(2-Fluorophenyl)pentan-3-yl]piperidine-4-carboxamide Hydrochloride (6d)** The title compound was prepared in the same manner as described for **6a** using **5d** instead of **5a**, in 62% yield. $^1\text{H-NMR}$ (DMSO- d_6) δ : 0.65 (6H, t, $J=7.6$ Hz), 1.60–1.73 (2H, m), 1.77–1.98 (4H, m), 2.08–2.18 (2H, m), 2.52–2.61 (1H, m), 2.76–2.90 (2H, m), 3.21–3.30 (2H, m), 7.01–7.12 (2H, m), 7.20–7.28 (2H, m), 7.82 (1H, s), 8.52 (1H, br s), 8.94 (1H, br s). MS (FAB) m/z : 293 ($\text{M}^+ + 1$).

***N*-[3-(3-Methoxyphenyl)pentan-3-yl]piperidine-4-carboxamide Hydrochloride (6e)** The title compound was prepared in the same manner as described for **6a** using **5e** instead of **5a**, in 66% yield. $^1\text{H-NMR}$ (DMSO- d_6) δ : 0.63 (6H, t, $J=7.6$ Hz), 1.65–1.73 (2H, m), 1.76–1.84 (4H, m), 1.90–2.08 (2H, m), 2.52–2.64 (1H, m), 2.78–2.90 (2H, m), 3.21–3.35 (2H, m), 3.72 (3H, s), 6.71–6.76 (2H, m), 6.83 (1H, d, $J=7.6$ Hz), 7.19 (1H, dd, $J=7.6$, 8.0 Hz), 7.72 (1H, s), 8.53 (1H, br s), 8.97 (1H, br s). MS (FAB) m/z : 305 ($\text{M}^+ + 1$).

***N*-[3-(2-Methoxyphenyl)pentan-3-yl]piperidine-4-carboxamide Hydrochloride (6f)** The title compound was prepared in the same manner as described for **6a** using **5f** instead of **5a**, in 69% yield. $^1\text{H-NMR}$ (DMSO- d_6) δ : 0.60 (6H, t, $J=7.6$ Hz), 1.64–1.73 (2H, m), 1.79–1.85 (2H, m), 2.00–2.16 (4H, m), 2.52–2.64 (1H, m), 2.78–2.88 (2H, m), 3.23–3.30 (2H, m), 3.74 (3H, s), 6.82–6.96 (2H, m), 7.10–7.22 (2H, m), 7.48 (1H, s), 8.45 (1H, br s), 8.80 (1H, br s). MS (FAB) m/z : 305 ($\text{M}^+ + 1$).

***N*-[3-(4-Fluorophenyl)pentan-3-yl]-1-(2-phenylethyl)piperidine-4-carboxamide Fumarate (3a)** To an ice-cooled mixture of **6a** (0.45 g, 1.37 mmol), phenylacetaldehyde (0.20 ml, 1.97 mmol), and sodium acetate (0.30 g, 3.66 mmol) in CH_2Cl_2 (10 ml) was added sodium triacetoxyborohydride (0.45 g, 2.12 mmol) and the mixture was stirred at room temperature for 15 h. The reaction mixture was concentrated *in vacuo* and partitioned between saturated aqueous sodium bicarbonate solution and CHCl_3 . The organic layer was dried over Na_2SO_4 and evaporated *in vacuo*. The resulting residue was purified by column chromatography on silica gel (MeOH/ CHCl_3 =3/97) to give *N*-[3-(4-fluorophenyl)pentan-3-yl]-1-(2-phenylethyl)-

piperidine-4-carboxamide (0.53 g) as a colorless solid. The compound was converted to its fumarate by treating it with fumaric acid (0.16 g, 1.38 mmol). The crude salt was suspended with CH_3CN and filtered to give the title compound **3a** (0.54 g, 76%) as a colorless powder. $^1\text{H-NMR}$ (DMSO- d_6) δ : 0.62 (6H, t, $J=7.2$ Hz), 1.55–1.69 (2H, m), 1.70–1.86 (4H, m), 1.96–2.08 (2H, m), 2.25–2.35 (2H, m), 2.35–2.45 (1H, m), 2.70–2.85 (4H, m), 3.17–3.26 (2H, m), 6.58 (2H, s), 7.08 (2H, dd, $J=8.4$, 8.8 Hz), 7.17–7.32 (7H, m), 7.67 (1H, s). MS (FAB) m/z : 397 ($\text{M}^+ + 1$). Anal. Calcd for $\text{C}_{25}\text{H}_{33}\text{N}_2\text{O}_4 \cdot \text{C}_4\text{H}_4\text{O}_4 \cdot 0.7\text{H}_2\text{O}$: C, 66.32; H, 7.37; N, 5.33; F, 3.62. Found: C, 66.39; H, 7.08; N, 5.14; F, 3.49.

***N*-(3-Phenylpentan-3-yl)-1-(2-phenylethyl)piperidine-4-carboxamide Fumarate (3b)** The title compound was prepared in the same manner as described for **3a** using **6b** instead of **6a**, in 83% yield. $^1\text{H-NMR}$ (DMSO- d_6) δ : 0.62 (6H, t, $J=7.2$ Hz), 1.56–1.69 (2H, m), 1.70–1.89 (4H, m), 1.97–2.09 (2H, m), 2.24–2.34 (2H, m), 2.36–2.46 (1H, m), 2.71–2.85 (4H, m), 3.12–3.21 (2H, m), 6.57 (2H, s), 7.12–7.32 (10H, m), 7.61 (1H, s). MS (FAB) m/z : 379 ($\text{M}^+ + 1$). Anal. Calcd for $\text{C}_{25}\text{H}_{34}\text{N}_2\text{O}_4 \cdot \text{C}_4\text{H}_4\text{O}_4 \cdot 0.2\text{H}_2\text{O}$: C, 69.91; H, 7.77; N, 5.62. Found: C, 69.82; H, 7.69; N, 5.44.

***N*-[3-(3-Fluorophenyl)pentan-3-yl]-1-(2-phenylethyl)piperidine-4-carboxamide Fumarate (3c)** The title compound was prepared in the same manner as described for **3a** using **6c** instead of **6a**, in 67% yield. $^1\text{H-NMR}$ (DMSO- d_6) δ : 0.63 (6H, t, $J=7.2$ Hz), 1.52–1.66 (2H, m), 1.67–1.87 (4H, m), 1.95–2.09 (2H, m), 2.17–2.28 (2H, m), 2.33–2.44 (1H, m), 2.65–2.83 (4H, m), 3.06–3.18 (2H, m), 6.59 (2H, s), 6.97–7.05 (2H, m), 7.08 (1H, d, $J=8.0$ Hz), 7.17–7.35 (6H, m), 7.69 (1H, s). MS (FAB) m/z : 397 ($\text{M}^+ + 1$). Anal. Calcd for $\text{C}_{25}\text{H}_{33}\text{N}_2\text{O}_4 \cdot 1.5\text{C}_4\text{H}_4\text{O}_4$: C, 66.25; H, 6.89; N, 4.91; F, 3.33. Found: C, 65.10; H, 6.99; N, 4.93; F, 3.40.

***N*-[3-(2-Fluorophenyl)pentan-3-yl]-1-(2-phenylethyl)piperidine-4-carboxamide Fumarate (3d)** The title compound was prepared in the same manner as described for **3a** using **6d** instead of **6a**, in 83% yield. $^1\text{H-NMR}$ (DMSO- d_6) δ : 0.65 (6H, t, $J=7.2$ Hz), 1.56–1.68 (2H, m), 1.69–1.75 (2H, m), 1.85–1.96 (2H, m), 2.07–2.18 (2H, m), 2.27–2.43 (3H, m), 2.73–2.86 (4H, m), 3.14–3.31 (2H, m), 6.58 (2H, s), 7.01–7.12 (2H, m), 7.17–7.32 (7H, m), 7.71 (1H, s). MS (FAB) m/z : 397 ($\text{M}^+ + 1$). Anal. Calcd for $\text{C}_{25}\text{H}_{33}\text{N}_2\text{O}_4 \cdot \text{C}_4\text{H}_4\text{O}_4 \cdot 0.2\text{H}_2\text{O}$: C, 67.47; H, 7.30; N, 5.43; F, 3.68. Found: C, 67.51; H, 7.30; N, 5.42; F, 3.57.

***N*-[3-(3-Methoxyphenyl)pentan-3-yl]-1-(2-phenylethyl)piperidine-4-carboxamide Fumarate (3e)** The title compound was prepared in the same manner as described for **3a** using **6e** instead of **6a**, in 81% yield. $^1\text{H-NMR}$ (DMSO- d_6) δ : 0.62 (6H, t, $J=7.2$ Hz), 1.53–1.66 (2H, m), 1.69–1.84 (4H, m), 1.95–2.05 (2H, m), 2.23–2.35 (2H, m), 2.38–2.48 (1H, m), 2.73–2.86 (4H, m), 3.12–3.20 (2H, m), 3.71 (3H, s), 6.58 (2H, s), 6.71–6.78 (2H, m), 6.83 (1H, d, $J=7.6$ Hz), 7.16–7.31 (6H, m), 7.59 (1H, s). MS (FAB) m/z : 409 ($\text{M}^+ + 1$). Anal. Calcd for $\text{C}_{26}\text{H}_{36}\text{N}_2\text{O}_4 \cdot \text{C}_4\text{H}_4\text{O}_4 \cdot 0.7\text{H}_2\text{O}$: C, 67.07; H, 7.77; N, 5.21. Found: C, 67.12; H, 7.51; N, 5.10.

***N*-[3-(2-Methoxyphenyl)pentan-3-yl]-1-(2-phenylethyl)piperidine-4-carboxamide Fumarate (3f)** The title compound was prepared in the same manner as described for **3a** using **6f** instead of **6a**, in 73% yield. $^1\text{H-NMR}$ (DMSO- d_6) δ : 0.60 (6H, t, $J=7.2$ Hz), 1.51–1.66 (2H, m), 1.69–1.76 (2H, m), 1.95–2.20 (4H, m), 2.23–2.34 (2H, m), 2.38–2.46 (1H, m), 2.70–2.82 (4H, m), 3.10–3.15 (2H, m), 3.74 (3H, s), 6.57 (2H, s), 6.85 (1H, dd, $J=6.8$, 8.0 Hz), 6.94 (1H, d, $J=8.0$ Hz), 7.10–7.31 (7H, m), 7.36 (1H, s). MS (FAB) m/z : 409 ($\text{M}^+ + 1$). Anal. Calcd for $\text{C}_{26}\text{H}_{36}\text{N}_2\text{O}_4 \cdot \text{C}_4\text{H}_4\text{O}_4 \cdot 0.4\text{H}_2\text{O}$: C, 67.75; H, 7.73; N, 5.27. Found: C, 67.84; H, 7.81; N, 5.30.

2-Ethyl-2-(4-methoxyphenyl)butanoic Acid (8) To an ice-cooled mixture of sodium hydride (60% dispersion in mineral oil; 1.30 g, 32.5 mmol) and iodoethane (3.0 ml, 37.3 mmol) in *N,N*-dimethylformamide (DMF) (30 ml) was added dropwise a solution of **7** (2.0 g, 13.6 mmol) and DMF (10 ml) and the mixture was stirred at room temperature for 20 h. The mixture was poured onto ice-water and then extracted with PhMe. The organic layer was washed with brine, dried over Na_2SO_4 , and evaporated *in vacuo*. The resulting residue was purified by column chromatography on silica gel (AcOEt/hexane=1/20) to give 2-ethyl-2-(4-methoxyphenyl)butanenitrile (2.68 g, 97%) as a colorless oil. To an ice-cooled solution of the nitrile obtained above (2.68 g, 13.2 mmol) in toluene (20 ml) was added dropwise DIBAL-H (1.01 M in toluene; 15 ml, 15.2 mmol) and the mixture was stirred at 0 °C for 16 h. The mixture was poured onto 1 M HCl aq. and then extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4 , and evaporated *in vacuo* to give 2-ethyl-2-(4-methoxyphenyl)butanal (2.68 g, 98%) as a colorless oil, which was used for the next step without further purification. To an ice-cooled mixture of the aldehyde obtained above (2.68 g, 13.0 mmol), $\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$ (3.0 g, 19.2 mmol), 2-methyl-2-butene (5.0 ml, 47.1 mmol), and H_2O (5.0 ml) in *t*BuOH (20 ml) was added NaClO_2 (80%; 1.80 g, 15.9 mmol) and the mixture was stirred at room temperature for 18 h.

The reaction mixture was concentrated *in vacuo* and partitioned between H₂O and AcOEt. The organic layer was washed with brine, dried over Na₂SO₄, and evaporated *in vacuo*. The residue was partitioned between 1 M NaOH aq. and Et₂O, the aqueous layer was acidified with HCl aq., and then extracted with AcOEt. The organic layer was washed with brine, dried over Na₂SO₄, and evaporated *in vacuo* to give the title compound **8** (2.26 g, 78%) as a colorless oil. ¹H-NMR (CDCl₃) δ : 0.77 (6H, t, *J*=7.6 Hz), 1.94–2.15 (4H, m), 3.80 (3H, s), 6.88 (2H, d, *J*=8.8 Hz), 7.24 (2H, d, *J*=8.8 Hz). MS (FAB) *m/z*: 221 (*M*⁺–1).

tert-Butyl 4-[[3-(4-Methoxyphenyl)pentan-3-yl]carbamoyl]piperidine-1-carboxylate (9) To a mixture of **8** (2.26 g, 10.2 mmol), BuOH (5.5 mL, 53.1 mmol), and Et₃N (2.0 mL, 14.3 mmol) in PhMe (20 mL) was added dropwise a solution of diphenylphosphoryl azide (3.5 g, 13.6 mmol) and PhMe (10 mL) and the mixture was stirred at 100 °C for 24 h. The mixture was poured onto ice-water and then extracted with PhMe. The organic layer was washed successively with saturated aqueous sodium bicarbonate solution and brine, dried over Na₂SO₄, and evaporated *in vacuo*. The resulting residue was purified by column chromatography on silica gel (AcOEt/hexane=1/8) to give benzyl [3-(4-methoxyphenyl)pentan-3-yl]carbamate (2.74 g, 82%) as a yellow oil. To a solution of the benzyl carbamate obtained above (2.74 g, 8.37 mmol) in AcOEt (20 mL) was added 10% Pd/C (10 w/w%; 0.50 g) and the mixture was stirred under hydrogen atmosphere at room temperature for 5 h. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to give 3-(4-methoxyphenyl)pentan-3-amine (1.53 g, 95%) as a colorless oil, which was used for the next step without further purification. To an ice-cooled mixture of the amine obtained above (1.53 g, 7.92 mmol), 1-(Boc)piperidine-4-carboxylic acid (1.90 g, 8.29 mmol), and HOBt (1.10 g, 8.14 mmol) in CH₃CN (20 mL) was added WSCD (1.60 g, 8.36 mmol) and the mixture was stirred at room temperature for 20 h. The reaction mixture was concentrated *in vacuo* and partitioned between H₂O and AcOEt. The organic layer was washed successively with 5% aqueous citric acid solution, saturated aqueous sodium bicarbonate solution, and brine, dried over Na₂SO₄, and evaporated *in vacuo*. The resulting residue was purified by column chromatography on silica gel (AcOEt/hexane=1/2) to give the title compound **9** (2.41 g, 75%) as a colorless foam. ¹H-NMR (CDCl₃) δ : 0.70 (6H, t, *J*=7.2 Hz), 1.45 (9H, s), 1.57–1.70 (2H, m), 1.80–1.95 (2H, m), 1.99–2.16 (4H, m), 2.22–2.32 (1H, m), 2.71–2.91 (2H, m), 3.79 (3H, s), 4.11–4.19 (2H, m), 5.50 (1H, s), 6.86 (2H, d, *J*=8.8 Hz), 7.18 (2H, d, *J*=8.8 Hz). MS (FAB) *m/z*: 405 (*M*⁺+1).

N-[3-(4-Methoxyphenyl)pentan-3-yl]-1-(2-phenylethyl)piperidine-4-carboxamide Fumarate (3g) To an ice-cooled solution of **9** (2.41 g, 5.96 mmol) in AcOEt (10 mL) was added 4 M HCl–AcOEt (10 mL, 40.0 mmol) and the mixture was stirred at room temperature for 16 h. After concentration of the reaction mixture, the resulting solid was suspended with AcOEt and collected by filtration to give *N*-[3-(4-methoxyphenyl)pentan-3-yl]piperidine-4-carboxamide hydrochloride (1.80 g, 89%) as a light yellow solid. The title compound was prepared in the same manner as described for **3a** using *N*-[3-(4-methoxyphenyl)pentan-3-yl]piperidine-4-carboxamide hydrochloride instead of **6a**, in 64% yield. ¹H-NMR (DMSO-*d*₆) δ : 0.61 (6H, t, *J*=7.2 Hz), 1.50–1.64 (2H, m), 1.66–1.74 (2H, m), 1.74–1.86 (2H, m), 1.95–2.08 (2H, m), 2.10–2.23 (2H, m), 2.30–2.41 (1H, m), 2.62–2.70 (2H, m), 2.73–2.82 (2H, m), 3.04–3.14 (2H, m), 3.72 (3H, s), 6.58 (2H, s), 6.82 (2H, d, *J*=8.0 Hz), 7.12–7.32 (7H, m), 7.51 (1H, s). MS (FAB) *m/z*: 409 (*M*⁺+1). *Anal.* Calcd for C₂₆H₃₆N₂O₂·C₄H₄O₄·0.5H₂O: C, 67.52; H, 7.74; N, 5.25. Found: C, 67.70; H, 7.68; N, 5.34.

1-(4-Fluorophenyl)cyclopentanecarboxylic Acid (11) To an ice-cooled solution of **10** (5.0 g, 37.0 mmol) and 1,4-dibromobutane (4.7 mL, 39.8 mmol) in DMF (50 mL) was added portionwise sodium hydride (60% dispersion in mineral oil; 3.2 g, 80.0 mmol) and the mixture was stirred at room temperature for 3 h. The mixture was poured onto ice-water and then extracted with PhMe. The organic layer was washed with brine, dried over Na₂SO₄, and evaporated *in vacuo*. The residue was partitioned between 1 M NaOH aq. and Et₂O, the aqueous layer was acidified with HCl aq., and then extracted with AcOEt. The organic layer was washed with brine, dried over Na₂SO₄, and evaporated *in vacuo* to give the title compound **11** (6.65 g, 93%) as a colorless solid. ¹H-NMR (CDCl₃) δ : 1.71–1.79 (4H, m), 1.83–1.94 (2H, m), 2.60–2.70 (2H, m), 6.99 (2H, dd, *J*=8.8, 8.8 Hz), 7.35 (2H, dd, *J*=4.8, 8.8 Hz). MS (FAB)

m/z: 207 (*M*⁺–1).

Benzyl 4-[[1-(4-Fluorophenyl)cyclopentyl]carbamoyl]piperidine-1-carboxylate (12) To a mixture of **11** (1.0 g, 4.80 mmol), BuOH (3.0 mL, 29.0 mmol), and Et₃N (1.5 mL, 10.8 mmol) in PhMe (10 mL) was added dropwise a solution of diphenylphosphoryl azide (1.7 g, 6.18 mmol) and PhMe (5.0 mL) and the mixture was stirred at 100 °C for 24 h. The mixture was poured onto ice-water and then extracted with PhMe. The organic layer was washed successively with saturated aqueous sodium bicarbonate solution and brine, dried over Na₂SO₄, and evaporated *in vacuo*. The resulting residue was purified by column chromatography on silica gel (AcOEt/hexane=1/8) to give benzyl [1-(4-fluorophenyl)cyclopentyl]carbamate (1.32 g, 88%) as a colorless solid. To a solution of the benzyl carbamate obtained above (1.32 g, 4.21 mmol) in AcOEt (15 mL) was added 10% Pd/C (10 w/w%; 0.20 g) and the mixture was stirred under hydrogen atmosphere at room temperature for 4 h. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to give 1-(4-fluorophenyl)cyclopentanamine (0.75 g) as a colorless oil, which was used for the next step without further purification. To a solution of 1-(Cbz)piperidine-4-carboxylic acid (1.28 g, 4.86 mmol) and DMF (1 drop) in CH₂Cl₂ (20 mL) was added (COCl)₂ (0.80 mL, 9.79 mmol) and the mixture was stirred at room temperature for 6 h. The reaction mixture was concentrated *in vacuo* to give the corresponding acid chloride as a colorless oil, which was used for the next step without further purification. To an ice-cooled solution of the amine obtained above (0.75 g) and Et₃N (1.4 mL, 10.0 mmol) in CH₂Cl₂ (10 mL) was added a solution of the acid chloride obtained above and CH₂Cl₂ (10 mL) and the mixture was stirred at room temperature for 24 h. The reaction mixture was concentrated *in vacuo* and partitioned between H₂O and AcOEt. The organic layer was washed successively with 5% aqueous citric acid solution, saturated aqueous sodium bicarbonate solution, and brine, dried over Na₂SO₄, and evaporated *in vacuo*. The resulting residue was purified by column chromatography on silica gel (AcOEt/hexane=1/1) to give the title compound **12** (1.49 g, 2 steps 83%) as a colorless foam. ¹H-NMR (CDCl₃) δ : 1.52–1.65 (2H, m), 1.72–1.85 (6H, m), 1.98–2.10 (2H, m), 2.15–2.23 (1H, m), 2.28–2.36 (2H, m), 2.76–2.90 (2H, m), 4.10–4.27 (2H, m), 5.11 (2H, s), 5.61 (1H, s), 6.97 (2H, dd, *J*=8.8, 8.8 Hz), 7.29–7.38 (7H, m). MS (FAB) *m/z*: 425 (*M*⁺+1).

N-[1-(4-Fluorophenyl)cyclopentyl]-1-(2-phenylethyl)piperidine-4-carboxamide Fumarate (13) To a solution of **12** (1.49 g, 3.51 mmol) in EtOH (20 mL) was added 10% Pd/C (10 w/w%; 0.20 g) and the mixture was stirred under hydrogen atmosphere at room temperature for 2 h. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to give *N*-[1-(4-fluorophenyl)cyclopentyl]piperidine-4-carboxamide (1.0 g, 98%) as a colorless solid, which was used for the next step without further purification. To an ice-cooled solution of the amine obtained above (0.30 g, 1.03 mmol), phenylacetaldehyde (0.20 mL, 1.79 mmol), and AcOH (0.50 mL) in CH₂Cl₂ (10 mL) was added sodium triacetoxyborohydride (0.40 g, 1.89 mmol) and the mixture was stirred at room temperature for 15 h. The reaction mixture was concentrated *in vacuo* and partitioned between saturated aqueous sodium bicarbonate solution and CHCl₃. The organic layer was dried over Na₂SO₄ and evaporated *in vacuo*. The resulting residue was purified by column chromatography on silica gel (MeOH/CHCl₃=3/97) to give *N*-[1-(4-fluorophenyl)cyclopentyl]-1-(2-phenylethyl)piperidine-4-carboxamide (0.45 g) as a colorless solid. The compound was converted to its fumarate by treating it with fumaric acid (0.12 g, 1.03 mmol). The crude salt was suspended with CH₃CN and filtered to give the title compound **13** (0.47 g, 90%) as a colorless powder. ¹H-NMR (DMSO-*d*₆) δ : 1.48–1.61 (2H, m), 1.62–1.76 (6H, m), 1.76–1.86 (2H, m), 2.12–2.34 (5H, m), 2.61–2.70 (2H, m), 2.73–2.82 (2H, m), 3.02–3.13 (2H, m), 6.58 (2H, s), 7.07 (2H, dd, *J*=8.8, 8.8 Hz), 7.15–7.36 (7H, m), 7.94 (1H, s). MS (FAB) *m/z*: 395 (*M*⁺+1). *Anal.* Calcd for C₂₅H₃₁N₂O₂·C₄H₄O₄·1.5H₂O: C, 64.79; H, 7.12; N, 5.21; F, 3.53. Found: C, 64.62; H, 7.14; N, 5.21; F, 3.51.

(1R)-1-(4-Fluorophenyl)-2-methylpropan-1-amine Hydrochloride (15) To a mixture of **14**⁴⁴ (13.2 g, 67.3 mmol) and Et₃N (12 mL, 86.0 mmol) in *t*BuOH (150 mL) was added dropwise diphenylphosphoryl azide (20 g, 72.7 mmol) and the mixture was stirred at 100 °C for 20 h. The mixture was poured onto ice-water and then extracted with PhMe. The organic layer was washed successively with saturated aqueous sodium bicarbonate solution and brine, dried over Na₂SO₄, and evaporated *in vacuo* to give *tert*-butyl [(1R)-1-(4-fluorophenyl)-2-methylpropyl]carbamate (19.6 g) as a light yellow solid. To an ice-cooled mixture of the *N*-Boc derivative obtained above (19.6 g) in AcOEt (100 mL) was added 4 M HCl–AcOEt (100 mL, 400 mmol) and the mixture was stirred at room temperature for 16 h. After concentration of the reaction mixture, the resulting solid was suspended with AcOEt and collected by filtration to give the title compound **15** (11.3 g, 2 steps

82%) as a colorless solid. $[\alpha]_D^{25} -4.45$ ($c=1.00$, H_2O). 1H -NMR (DMSO- d_6) δ : 0.69 (3H, d, $J=7.2$ Hz), 1.02 (3H, d, $J=7.2$ Hz), 2.08—2.22 (1H, m), 3.99 (1H, d, $J=8.4$ Hz), 7.27 (2H, dd, $J=8.2$, 8.4 Hz), 7.53 (2H, dd, $J=5.6$, 8.4 Hz), 8.60 (3H, s). MS (FAB) m/z : 168 ($M^+ + 1$).

***N*-[*(1R)*-1-(4-Fluorophenyl)-2-methylpropyl]piperidine-4-carboxamide Hydrochloride (16)** To an ice-cooled mixture of **15** (10.4 g, 51.1 mmol), Et_3N (15 ml, 108 mmol), 1-(Boc)piperidine-4-carboxylic acid (12 g, 52.3 mmol), and HOBt (7.0 g, 50.7 mmol) in CH_3CN (100 ml) was added WSCD (10.5 g, 54.9 mmol) and the mixture was stirred at room temperature for 3 d. The reaction mixture was concentrated *in vacuo* and partitioned between H_2O and AcOEt. The organic layer was washed successively with 5% aqueous citric acid solution, saturated aqueous sodium bicarbonate solution, and brine, dried over Na_2SO_4 , and evaporated *in vacuo* to give *tert*-butyl 4-[[*(1R)*-1-(4-fluorophenyl)-2-methylpropyl]carbamoyl]piperidine-1-carboxylate (19.5 g) as a colorless foam. To an ice-cooled solution of the *N*-Boc derivative obtained above (19.5 g) in AcOEt (100 ml) was added 4 M HCl-AcOEt (100 ml, 400 mmol) and the mixture was stirred at room temperature for 16 h. After concentration of the reaction mixture, the resulting solid was suspended with acetone and collected by filtration to give the title compound **16** (15.5 g, 2 steps 96%) as a colorless solid. 1H -NMR (DMSO- d_6) δ : 0.69 (3H, d, $J=6.4$ Hz), 0.88 (3H, d, $J=6.4$ Hz), 1.58—1.81 (3H, m), 1.84—1.97 (2H, m), 2.52—2.57 (1H, m), 2.75—2.92 (2H, m), 3.18—3.31 (2H, m), 4.51 (1H, dd, $J=8.8$, 8.8 Hz), 7.13 (2H, dd, $J=8.0$, 8.4 Hz), 7.31 (2H, dd, $J=5.6$, 8.0 Hz), 8.38 (1H, d, $J=8.8$ Hz), 8.61 (1H, br s), 9.04 (1H, br s). MS (FAB) m/z : 279 ($M^+ + 1$).

***N*-[*(1R)*-1-(4-Fluorophenyl)-2-methylpropyl]-1-(2-phenylethyl)piperidine-4-carboxamide Hydrochloride (17a) (Method A)** To an ice-cooled mixture of **16** (0.34 g, 1.08 mmol), phenylacetaldehyde (0.20 ml, 1.79 mmol), and AcONa (0.10 g, 1.22 mmol) in CH_2Cl_2 (10 ml) was added sodium triacetoxyborohydride (0.46 g, 2.17 mmol) and the mixture was stirred at room temperature for 15 h. The reaction mixture was concentrated *in vacuo* and partitioned between saturated aqueous sodium bicarbonate solution and $CHCl_3$. The organic layer was dried over Na_2SO_4 and evaporated *in vacuo*. The resulting residue was purified by column chromatography on silica gel (MeOH/ $CHCl_3$ =3/97) to give *N*-[*(1R)*-1-(4-fluorophenyl)-2-methylpropyl]-1-(2-phenylethyl)piperidine-4-carboxamide (0.24 g) as a colorless solid. The compound was converted to its hydrochloride salt by treating it with 4 M HCl-AcOEt (0.20 ml, 800 μ mol). The crude salt was suspended with AcOEt and filtered to give the title compound **17a** (0.22 g, 53%) as a colorless powder. 1H -NMR (DMSO- d_6) δ : 0.70 (3H, d, $J=6.8$ Hz), 0.89 (3H, d, $J=6.8$ Hz), 1.78—2.07 (5H, m), 2.46—2.53 (1H, m), 2.85—2.96 (2H, m), 3.01—3.08 (2H, m), 3.22—3.30 (2H, m), 3.52—3.64 (2H, m), 4.53 (1H, dd, $J=8.4$, 9.2 Hz), 7.13 (2H, dd, $J=8.0$, 8.4 Hz), 7.23—7.38 (7H, m), 8.40 (1H, d, $J=9.2$ Hz), 10.36 and 10.74 (1H, br s). MS (FAB) m/z : 383 ($M^+ + 1$). *Anal.* Calcd for $C_{24}H_{31}N_2OF \cdot HCl \cdot 0.3H_2O$: C, 67.92; H, 7.74; N, 4.48; Cl, 8.35; F, 4.90. Found: C, 68.05; H, 7.61; N, 6.25; Cl, 8.32; F, 4.50.

***N*-[*(1S)*-1-(4-Fluorophenyl)-2-methylpropyl]-1-(2-phenylethyl)piperidine-4-carboxamide Hydrochloride (*ent*-17a)** The title compound was prepared in the same manner as described in Chart 4 using (2*S*)-2-(4-fluorophenyl)-3-methylbutanoic acid instead of **14**.

***N*-[*(1R)*-1-(4-Fluorophenyl)-2-methylpropyl]-1-[2-[2-(trifluoromethyl)phenyl]ethyl]piperidine-4-carboxamide Oxalate (17b)** The title compound was prepared in the same manner as described for **17a** using 2-trifluoromethylphenylacetaldehyde instead of phenylacetaldehyde, in 67% yield. 1H -NMR (DMSO- d_6) δ : 0.70 (3H, d, $J=6.8$ Hz), 0.89 (3H, d, $J=6.8$ Hz), 1.66—1.98 (5H, m), 2.41—2.51 (1H, m), 2.74—2.90 (2H, m), 3.11 (4H, br s), 3.37—3.50 (2H, m), 4.53 (1H, dd, $J=8.4$, 9.2 Hz), 7.13 (2H, dd, $J=8.0$, 8.4 Hz), 7.31 (2H, dd, $J=5.6$, 8.0 Hz), 7.48 (1H, dd, $J=7.6$, 8.4 Hz), 7.55 (1H, d, $J=7.6$ Hz), 7.67 (1H, dd, $J=7.6$, 7.6 Hz), 7.72 (1H, d, $J=8.4$ Hz), 8.30 (1H, d, $J=9.2$ Hz). MS (FAB) m/z : 451 ($M^+ + 1$). *Anal.* Calcd for $C_{25}H_{30}N_2OF_4 \cdot C_2H_2O_4 \cdot 0.2H_2O$: C, 59.60; H, 6.00; N, 5.15; F, 13.97. Found: C, 59.68; H, 6.00; N, 5.16; F, 13.91.

***N*-[*(1R)*-1-(4-Fluorophenyl)-2-methylpropyl]-1-[2-[3-(trifluoromethyl)phenyl]ethyl]piperidine-4-carboxamide Oxalate (17c)** The title compound was prepared in the same manner as described for **17a** using 3-trifluoromethylphenylacetaldehyde instead of phenylacetaldehyde, in 63% yield. 1H -NMR (DMSO- d_6) δ : 0.70 (3H, d, $J=6.8$ Hz), 0.89 (3H, d, $J=6.8$ Hz), 1.68—2.00 (5H, m), 2.43—2.53 (1H, m), 2.76—2.93 (2H, m), 3.02—3.11 (2H, m), 3.15—3.25 (2H, m), 3.38—3.52 (2H, m), 4.53 (1H, dd, $J=8.4$, 8.8 Hz), 7.13 (2H, dd, $J=8.0$, 8.4 Hz), 7.31 (2H, dd, $J=5.6$, 8.0 Hz), 7.53—7.68 (4H, m), 8.32 (1H, d, $J=8.8$ Hz). MS (FAB) m/z : 451 ($M^+ + 1$). *Anal.* Calcd for $C_{25}H_{30}N_2OF_4 \cdot C_2H_2O_4 \cdot 0.5H_2O$: C, 59.01; H, 6.05; N, 5.10; F, 13.83. Found: C, 59.01; H, 6.05; N, 5.09; F, 13.97.

***N*-[*(1R)*-1-(4-Fluorophenyl)-2-methylpropyl]-1-[2-[4-(trifluoromethyl)phenyl]ethyl]piperidine-4-carboxamide Oxalate (17d)** The title compound was prepared in the same manner as described for **17a** using 4-trifluoromethylphenylacetaldehyde instead of phenylacetaldehyde, in 65% yield. 1H -NMR (DMSO- d_6) δ : 0.70 (3H, d, $J=6.8$ Hz), 0.89 (3H, d, $J=6.8$ Hz), 1.65—1.98 (5H, m), 2.41—2.52 (1H, m), 2.70—2.90 (2H, m), 3.00—3.10 (2H, m), 3.12—3.23 (2H, m), 3.35—3.51 (2H, m), 4.53 (1H, dd, $J=8.4$, 8.4 Hz), 7.13 (2H, dd, $J=8.0$, 8.4 Hz), 7.30 (2H, dd, $J=5.6$, 8.0 Hz), 7.51 (2H, d, $J=8.4$ Hz), 7.70 (2H, d, $J=8.4$ Hz), 8.30 (1H, d, $J=8.4$ Hz). MS (FAB) m/z : 451 ($M^+ + 1$). *Anal.* Calcd for $C_{25}H_{30}N_2OF_4 \cdot C_2H_2O_4 \cdot 0.2H_2O$: C, 59.60; H, 6.00; N, 5.15; F, 13.97. Found: C, 59.61; H, 6.00; N, 5.13; F, 14.04.

***N*-[*(1R)*-1-(4-Fluorophenyl)-2-methylpropyl]-1-[2-(2-methoxyphenyl)ethyl]piperidine-4-carboxamide Fumarate (17e)** The title compound was prepared in the same manner as described for **17a** using 2-methoxyphenylacetaldehyde instead of phenylacetaldehyde, in 64% yield. 1H -NMR (DMSO- d_6) δ : 0.69 (3H, d, $J=6.8$ Hz), 0.88 (3H, d, $J=6.8$ Hz), 1.51—1.80 (4H, m), 1.83—1.97 (1H, m), 2.15—2.34 (3H, m), 2.59—2.68 (2H, m), 2.72—2.81 (2H, m), 3.04—3.16 (2H, m), 3.77 (3H, s), 4.52 (1H, dd, $J=8.4$, 9.2 Hz), 6.57 (2H, s), 6.86 (1H, dd, $J=7.6$, 7.6 Hz), 6.95 (1H, d, $J=8.0$ Hz), 7.08—7.22 (4H, m), 7.30 (2H, dd, $J=5.6$, 8.0 Hz), 8.17 (1H, d, $J=9.2$ Hz). MS (FAB) m/z : 413 ($M^+ + 1$). *Anal.* Calcd for $C_{25}H_{33}N_2O_2F \cdot C_4H_4O_4 \cdot 0.2H_2O$: C, 65.45; H, 7.08; N, 5.26; F, 3.57. Found: C, 65.35; H, 7.12; N, 5.29; F, 3.61.

***N*-[*(1R)*-1-(4-Fluorophenyl)-2-methylpropyl]-1-[2-(3-methoxyphenyl)ethyl]piperidine-4-carboxamide Oxalate (17f) (Method B)** To a mixture of **16** (0.41 g, 1.30 mmol) and K_2CO_3 (0.27 g, 1.95 mmol) in CH_3CN (10 ml) was added 2-(3-methoxyphenyl)ethyl *p*-toluenesulfonate (0.52 g, 1.70 mmol) and the mixture was stirred at 70 °C for 24 h. The reaction mixture was concentrated *in vacuo* and the resulting residue was partitioned between H_2O and $CHCl_3$. The organic layer was dried over Na_2SO_4 and evaporated *in vacuo*. The resulting residue was purified by column chromatography on silica gel (MeOH/ $CHCl_3$ =5/95) to give *N*-[*(1R)*-1-(4-fluorophenyl)-2-methylpropyl]-1-[2-(3-methoxyphenyl)ethyl]piperidine-4-carboxamide (0.45 g) as a colorless oil. The compound was converted to oxalate by treating it with oxalic acid (0.12 g, 1.31 mmol). The crude salt was suspended with acetone and filtered to give the title compound **17f** (0.46 g, 70%) as a colorless powder. 1H -NMR (DMSO- d_6) δ : 0.70 (3H, d, $J=6.8$ Hz), 0.89 (3H, d, $J=6.8$ Hz), 1.66—1.98 (5H, m), 2.42—2.54 (1H, m), 2.76—2.96 (4H, m), 3.09—3.20 (2H, m), 3.36—3.50 (2H, m), 3.74 (3H, s), 4.53 (1H, dd, $J=8.4$, 8.8 Hz), 6.78—6.86 (3H, m), 7.13 (2H, dd, $J=8.0$, 8.4 Hz), 7.23 (1H, dd, $J=7.6$, 7.6 Hz), 7.31 (2H, dd, $J=5.6$, 8.0 Hz), 8.31 (1H, d, $J=8.8$ Hz). MS (FAB) m/z : 413 ($M^+ + 1$). *Anal.* Calcd for $C_{25}H_{33}N_2O_2F \cdot C_4H_4O_4 \cdot 0.8H_2O$: C, 62.73; H, 7.14; N, 5.42; F, 3.67. Found: C, 62.95; H, 7.03; N, 5.47; F, 3.83.

***N*-[*(1R)*-1-(4-Fluorophenyl)-2-methylpropyl]-1-[2-(4-methoxyphenyl)ethyl]piperidine-4-carboxamide Fumarate (17g)** The title compound was prepared in the same manner as described for **17f** using 2-(4-methoxyphenyl)ethyl *p*-toluenesulfonate instead of 2-(3-methoxyphenyl)ethyl *p*-toluenesulfonate, in 89% yield. 1H -NMR (DMSO- d_6) δ : 0.69 (3H, d, $J=6.8$ Hz), 0.88 (3H, d, $J=6.8$ Hz), 1.51—1.80 (4H, m), 1.83—1.97 (1H, m), 2.15—2.33 (3H, m), 2.62—2.77 (4H, m), 3.05—3.16 (2H, m), 3.71 (3H, s), 4.52 (1H, dd, $J=8.4$, 9.2 Hz), 6.57 (2H, s), 6.84 (2H, d, $J=8.0$ Hz), 7.09—7.16 (4H, m), 7.30 (2H, dd, $J=5.6$, 8.0 Hz), 8.18 (1H, d, $J=9.2$ Hz). MS (FAB) m/z : 413 ($M^+ + 1$). *Anal.* Calcd for $C_{25}H_{33}N_2O_2F \cdot C_4H_4O_4$: C, 65.89; H, 7.06; N, 5.30; F, 3.59. Found: C, 65.53; H, 7.11; N, 5.25; F, 3.59.

1-[2-(2,3-Dimethoxyphenyl)ethyl]-*N*-[*(1R)*-1-(4-fluorophenyl)-2-methylpropyl]piperidine-4-carboxamide Oxalate (17h) The title compound was prepared in the same manner as described for **17a** using 2,3-dimethoxyphenylacetaldehyde instead of phenylacetaldehyde, in 50% yield. 1H -NMR (DMSO- d_6) δ : 0.70 (3H, d, $J=6.8$ Hz), 0.89 (3H, d, $J=6.8$ Hz), 1.66—1.99 (5H, m), 2.42—2.52 (1H, m), 2.77—2.96 (4H, m), 3.04—3.13 (2H, m), 3.39—3.54 (2H, m), 3.74 (3H, s), 3.79 (3H, s), 4.53 (1H, dd, $J=8.4$, 8.8 Hz), 6.81 (1H, dd, $J=1.6$, 7.6 Hz), 6.95 (1H, dd, $J=1.6$, 8.4 Hz), 7.02 (1H, dd, $J=7.6$, 8.4 Hz), 7.13 (2H, dd, $J=8.0$, 8.4 Hz), 7.30 (2H, dd, $J=5.6$, 8.0 Hz), 8.32 (1H, d, $J=8.8$ Hz). MS (FAB) m/z : 443 ($M^+ + 1$). *Anal.* Calcd for $C_{26}H_{35}N_2O_3F \cdot C_2H_2O_4 \cdot 0.5H_2O$: C, 62.09; H, 7.07; N, 5.17; F, 3.51. Found: C, 61.95; H, 7.03; N, 5.12; F, 3.53.

1-[2-(3,4-Dimethoxyphenyl)ethyl]-*N*-[*(1R)*-1-(4-fluorophenyl)-2-methylpropyl]piperidine-4-carboxamide Oxalate (17i) The title compound was prepared in the same manner as described for **17a** using 3,4-dimethoxyphenylacetaldehyde instead of phenylacetaldehyde, in 32% yield. 1H -NMR (DMSO- d_6) δ : 0.70 (3H, d, $J=6.8$ Hz), 0.89 (3H, d, $J=6.8$ Hz), 1.68—2.00 (5H, m), 2.43—2.53 (1H, m), 2.77—2.94 (4H, m), 3.11—3.20

(2H, m), 3.38—3.52 (2H, m), 3.72 (3H, s), 3.74 (3H, s), 4.53 (1H, dd, $J=8.4, 8.8$ Hz), 6.76 (1H, dd, $J=2.0, 8.0$ Hz), 6.86—6.91 (2H, m), 7.13 (2H, dd, $J=8.0, 8.4$ Hz), 7.30 (2H, dd, $J=5.6, 8.0$ Hz), 8.32 (1H, d, $J=8.8$ Hz). MS (FAB) m/z : 443 ($M^+ + 1$). Anal. Calcd for $C_{26}H_{35}N_2O_3F \cdot C_2H_5O_4 \cdot H_2O$: C, 61.08; H, 7.14; N, 5.09; F, 3.45. Found: C, 61.09; H, 7.06; N, 5.07; F, 3.49.

1-[2-(3,5-Dimethoxyphenyl)ethyl]-N-[(1R)-1-(4-fluorophenyl)-2-methylpropyl]piperidine-4-carboxamide Oxalate (17j) The title compound was prepared in the same manner as described for **17a** using 3,5-dimethoxyphenylacetaldehyde instead of phenylacetaldehyde, in 14% yield. 1H -NMR (DMSO- d_6) δ : 0.70 (3H, d, $J=6.8$ Hz), 0.89 (3H, d, $J=6.8$ Hz), 1.66—1.98 (5H, m), 2.42—2.53 (1H, m), 2.74—2.94 (4H, m), 3.12—3.21 (2H, m), 3.38—3.52 (2H, m), 3.73 (6H, s), 4.53 (1H, dd, $J=8.4, 8.8$ Hz), 6.38 (1H, t, $J=2.0$ Hz), 6.43 (2H, d, $J=2.0$ Hz), 7.13 (2H, dd, $J=8.0, 8.4$ Hz), 7.30 (2H, dd, $J=5.6, 8.0$ Hz), 8.31 (1H, d, $J=8.8$ Hz). MS (FAB) m/z : 443 ($M^+ + 1$). Anal. Calcd for $C_{26}H_{35}N_2O_3F \cdot C_2H_5O_4 \cdot 0.3H_2O$: C, 62.51; H, 7.04; N, 5.21; F, 3.53. Found: C, 62.53; H, 7.07; N, 5.15; F, 3.55.

1-[2-(2,5-Dimethoxyphenyl)ethyl]-N-[(1R)-1-(4-fluorophenyl)-2-methylpropyl]piperidine-4-carboxamide Oxalate (17k) The title compound was prepared in the same manner as described for **17a** using 2,5-dimethoxyphenylacetaldehyde instead of phenylacetaldehyde, in 71% yield. 1H -NMR (DMSO- d_6) δ : 0.70 (3H, d, $J=6.4$ Hz), 0.89 (3H, d, $J=6.4$ Hz), 1.66—1.98 (5H, m), 2.42—2.52 (1H, m), 2.73—2.93 (4H, m), 3.02—3.12 (2H, m), 3.35—3.50 (2H, m), 3.69 (3H, s), 3.74 (3H, s), 4.52 (1H, dd, $J=8.4, 9.2$ Hz), 6.77—6.85 (2H, m), 6.91 (1H, d, $J=8.4$ Hz), 7.13 (2H, dd, $J=8.0, 8.4$ Hz), 7.30 (2H, dd, $J=5.6, 8.0$ Hz), 8.31 (1H, d, $J=9.2$ Hz). MS (FAB) m/z : 443 ($M^+ + 1$). Anal. Calcd for $C_{26}H_{35}N_2O_3F \cdot C_2H_5O_4 \cdot H_2O$: C, 63.14; H, 7.00; N, 5.26; F, 3.57. Found: C, 63.35; H, 7.06; N, 5.26; F, 3.64.

Ethyl [3-(2-Oxoethyl)phenoxy]acetate (19a) To an ice-cooled mixture of **18** (1.0 g, 8.19 mmol) and K_2CO_3 (1.4 g, 10.1 mmol) in CH_3CN (10 ml) was added ethyl bromoacetate (1.5 g, 9.98 mmol) and the mixture was stirred at room temperature for 24 h. The reaction mixture was concentrated *in vacuo* and the resulting residue was partitioned between H_2O and AcOEt. The organic layer was washed with brine, dried over Na_2SO_4 , and evaporated *in vacuo*. The resulting residue was purified by column chromatography on silica gel (AcOEt/hexane=1/4) to give ethyl [3-(formylphenoxy)acetate] (1.7 g, 100%) as a colorless oil. To an ice-cooled mixture of (methoxymethyl)-triphenylphosphonium chloride (5.0 g, 14.6 mmol) in THF (50 ml) was added *t*BuOK (1.6 g, 14.3 mmol) and the mixture was stirred at 0 °C for 10 min. To this ice-cooled mixture was added the aldehyde obtained above (1.7 g, 8.16 mmol) and the mixture was stirred at room temperature for 30 min. The mixture was poured into ice-water and then extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4 , and evaporated *in vacuo*. The resulting residue was purified by column chromatography on silica gel ($CHCl_3$ /hexane=1/4) to give ethyl [3-(2-methoxyvinyl)phenoxy]acetate (1.11 g, 58%) as a yellow oil. To the methyl ether obtained above (1.11 g, 4.70 mmol) was added formic acid (10 ml) and the mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated *in vacuo* and the resulting residue was partitioned between H_2O and AcOEt. The organic layer was washed with brine, dried over Na_2SO_4 , and evaporated *in vacuo* to give the title compound **19a** (1.0 g, 96%) as a yellow oil. This compound was directly used for the next step.

[3-(2-Methoxyethoxy)phenyl]acetaldehyde (19b) The title compound was prepared in the same manner as described for **19a** using 2-bromoethyl methyl ether instead of ethyl bromoacetate, in 97% yield. 1H -NMR ($CDCl_3$) δ : 3.45 (3H, s), 3.64 (2H, d, $J=2.0$ Hz), 3.75 (2H, t, $J=4.8$ Hz), 4.12 (2H, t, $J=4.8$ Hz), 6.79—6.83 (2H, m), 6.87 (1H, dd, $J=2.8, 7.6$ Hz), 7.25—7.30 (1H, m), 9.73 (1H, t, $J=2.0$ Hz). MS (EI) m/z : 194 (M^+).

Ethyl [3-[2-(4-[(1R)-1-(4-Fluorophenyl)-2-methylpropyl]carbamoyl]-piperidin-1-yl)ethyl]phenoxy]acetate Oxalate (17l) The title compound was prepared in the same manner as described for **17a** using **19a** instead of phenylacetaldehyde, in 23% yield. 1H -NMR (DMSO- d_6) δ : 0.70 (3H, d, $J=6.8$ Hz), 0.89 (3H, d, $J=6.8$ Hz), 1.21 (3H, t, $J=7.2$ Hz), 1.65—1.98 (5H, m), 2.42—2.54 (1H, m), 2.72—2.96 (4H, m), 3.10—3.22 (2H, m), 3.36—3.51 (2H, m), 4.12 (2H, q, $J=7.2$ Hz), 4.53 (1H, dd, $J=8.4, 8.8$ Hz), 4.76 (2H, s), 6.80 (1H, dd, $J=2.4, 8.0$ Hz), 6.84—6.89 (2H, m), 7.13 (2H, dd, $J=8.0, 8.4$ Hz), 7.24 (1H, dd, $J=8.0, 8.0$ Hz), 7.30 (2H, dd, $J=5.6, 8.0$ Hz), 8.30 (1H, d, $J=8.8$ Hz). MS (FAB) m/z : 485 ($M^+ + 1$). Anal. Calcd for $C_{28}H_{37}N_2O_4F \cdot C_2H_5O_4 \cdot C$, 62.70; H, 6.84; N, 4.87; F, 3.31. Found: C, 62.34; H, 6.82; N, 4.75; F, 3.30.

N-[(1R)-1-(4-Fluorophenyl)-2-methylpropyl]-1-[2-[3-(2-methoxyethoxy)phenyl]ethyl]piperidine-4-carboxamide Hydrochloride (17m) The title compound was prepared in the same manner as described for **17a** using **19b** instead of phenylacetaldehyde, in 72% yield. 1H -NMR (DMSO-

d_6) δ : 0.70 (3H, d, $J=6.8$ Hz), 0.89 (3H, d, $J=6.8$ Hz), 1.78—2.08 (5H, m), 2.45—2.54 (1H, m), 2.80—3.06 (4H, m), 3.20—3.32 (2H, m), 3.31 (3H, s), 3.50—3.62 (2H, m), 3.62—3.68 (2H, m), 4.05—4.11 (2H, m), 4.53 (1H, dd, $J=8.4, 8.8$ Hz), 6.80—6.90 (3H, m), 7.13 (2H, dd, $J=8.0, 8.4$ Hz), 7.24 (1H, dd, $J=7.6, 7.6$ Hz), 7.32 (2H, dd, $J=5.6, 8.0$ Hz), 8.41 (1H, d, $J=8.8$ Hz), 10.37 and 10.74 (1H, s). MS (FAB) m/z : 457 ($M^+ + 1$). Anal. Calcd for $C_{27}H_{37}N_2O_3F \cdot HCl \cdot 0.2H_2O$: C, 65.29; H, 7.72; N, 5.64; Cl, 7.14; F, 3.83. Found: C, 65.32; H, 7.90; N, 5.65; Cl, 7.13; F, 3.83.

N-[(1R)-1-(4-Fluorophenyl)-2-methylpropyl]-1-[2-[3-(2-hydroxyethoxy)phenyl]ethyl]piperidine-4-carboxamide Hydrochloride (17n) To a mixture of **17l** (0.20 g, 348 μ mol) in $CHCl_3$ (10 ml) was added saturated aqueous sodium bicarbonate solution (10 ml) and the mixture was stirred at room temperature for 15 min. The organic layer was separated, dried over Na_2SO_4 , and evaporated *in vacuo* to give ethyl [3-[2-(4-[(1R)-1-(4-fluorophenyl)-2-methylpropyl]carbamoyl]piperidin-1-yl)ethyl]phenoxy]acetate (0.17 g) as a colorless foam, which was used for the next step without further purification. To a solution of the ester obtained above (0.17 g, 348 μ mol) in THF (10 ml) was added $LiAlH_4$ (40 mg, 1.05 mmol) at -40 °C and the mixture was gradually warmed to 0 °C for 2 h. The reaction was quenched with $Na_2SO_4 \cdot 10H_2O$ (1.0 g) and stirred at room temperature for 15 h. The precipitate was removed by filtration and the filtrate was concentrated *in vacuo*. The resulting residue was purified by column chromatography on silica gel (MeOH/ $CHCl_3$ =10/90) to give *N*-[(1R)-1-(4-fluorophenyl)-2-methylpropyl]-1-[2-[3-(2-hydroxyethoxy)phenyl]ethyl]piperidine-4-carboxamide (0.18 g) as a colorless oil. The compound was converted to its hydrochloride salt by treating it with 4 M HCl-AcOEt (0.20 ml, 800 μ mol). The crude salt was suspended with acetone and filtered to give the title compound **17n** (89 mg, 53%) as a colorless powder. 1H -NMR (DMSO- d_6) δ : 0.70 (3H, d, $J=6.8$ Hz), 0.89 (3H, d, $J=6.8$ Hz), 1.76—2.07 (5H, m), 2.45—2.54 (1H, m), 2.82—3.06 (4H, m), 3.20—3.32 (2H, m), 3.51—3.62 (2H, m), 3.67—3.74 (2H, m), 3.97 (2H, t, $J=5.2$ Hz), 4.53 (1H, dd, $J=8.4, 9.2$ Hz), 4.88 (1H, s), 6.80—6.89 (3H, m), 7.13 (2H, dd, $J=8.0, 8.4$ Hz), 7.24 (1H, dd, $J=7.6, 7.6$ Hz), 7.32 (2H, dd, $J=5.6, 8.0$ Hz), 8.40 (1H, d, $J=9.2$ Hz), 10.31 and 10.68 (1H, s). MS (FAB) m/z : 443 ($M^+ + 1$). Anal. Calcd for $C_{26}H_{35}N_2O_3F \cdot HCl \cdot 0.3H_2O$: C, 64.46; H, 7.62; N, 5.78; Cl, 7.32; F, 3.92. Found: C, 64.53; H, 7.55; N, 5.80; Cl, 7.46; F, 3.93.

T-Type Ca^{2+} Channel-Blocking Activity Study HEK293 cells stably expressing human Cav3.1 ($\alpha 1G$) were maintained in D-MEM supplemented with 10% (v/v) fetal bovine serum, penicillin (100 U/ml), streptomycin (100 μ g/ml), geneticin (600 μ g/ml) at 37 °C in a humid atmosphere of 5% CO_2 and 95% air. One day prior to performing the assay, cells were plated into black-walled poly-D-lysine-coated 96-well assay plates at 25000 cells/well. Hanks balanced salt solution, containing 1.3 mM $CaCl_2$, 20 mM *N*-(2-hydroxyethyl)piperazine-*N'*-2-ethanesulfonic acid (HEPES) and 2.5 mM probenecid was used as the assay buffer. The growth medium was removed and replaced with dye loading buffer (100 μ l/well) containing 4 μ M fluo-3 AM, 0.04% Pluronic acid F-127, and 1% fetal bovine serum in the assay buffer. After one-hour incubation in dye loading buffer, the cells were washed four times with the assay buffer using an automated cell washer, giving a final volume of 100 μ l of assay buffer in each well. The plates were left to stand at room temperature for 10 min before assay, after which the plates were placed into a FLIPRTM apparatus (Molecular Devices, Berkshire, U.K.) to monitor cell fluorescence. Test compounds (50 μ l each) were added to each well, and the decrease in intercellular calcium concentrations as area under the curve (*AUC*) was detected up to 5 min after addition of test compounds. The maximum decrease, expressed as 100% inhibition was achieved with mibefradil at 3+ μ M. The IC_{50} value was calculated using a nonlinear regression method, taking the maximum reaction value as 100%.

Pharmacology *in Vitro* Study Male Hartley guinea pigs (250—400 g) were sacrificed by decapitation under isoflurane anesthesia, and their hearts were quickly removed. Right atria were dissected and mounted vertically in a 30-ml organ bath containing Tyrode solution (130 mM NaCl, 5.6 mM KCl, 2.15 mM $CaCl_2 \cdot 2H_2O$, 1.1 mM $MgCl_2 \cdot 6H_2O$, 0.6 mM $NaH_2PO_4 \cdot 2H_2O$, 11 mM D-glucose, 20 mM $NaHCO_3$) at 37 °C and bubbled with 95% O_2 and 5% CO_2 . The resting tension on the muscles was approximately 1 g and was kept constant throughout the experiments. Under these conditions, the right atria were allowed to equilibrate for 60 min with exchange of bath solution every 20 min before drug administration. Amplitude of constriction was measured isometrically using a force-displacement transducer (Nihon Kohden SB-1T) to obtain the spontaneous beat rate with a tachometer (Nihon Kohden AT-600G) that was triggered by the contractile pulse. After the initial spontaneous beat rate was recorded, test compounds dissolved in dimethyl sulfoxide (DMSO) and diluted with saline to the desired concentration were added to the bath solution cumulatively at 30-min intervals to construct a concen-

tration–response curve. The EC₃₀ value for the concentration of the compounds producing a 30% reduction from initial spontaneous beat rate was determined via linear regression.

Pharmacology in Vivo Study (per os (p.o.)) Male SHR rats (300–350 g) were anesthetized with pentobarbital (60 mg/kg intraperitoneally (i.p.)), and a polyethylene cannula (PE-50) was implanted in the common carotid artery with the opposite end of the catheter then routed to an exit site at the back of the neck. Animals were allowed a one- to two-day recovery period after the operation, during which time they were housed individually with free access to rat chow and water. Blood pressure was measured using a pressure transducer (Nihon Kohden DX-100) coupled to the carotid artery cannula and a pressure amplifier (Nihon Kohden AP-621G) and was continuously recorded using a polygraph system. Heart rate was measured with a cardiatachometer (Nihon Kohden AT-600G) triggered by the blood pressure pulsewave. After a 30-min measurement period to establish baseline values, test compounds were orally administrated as an aqueous solution by gavage at 10 and 30 mg/kg (salt form).

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References

- Brini M., Carafoli E., *Cell. Mol. Life Sci.*, **57**, 354–370 (2000).
- Catterall W. A., Perez-Reyes E., Snutch T. P., Striessnig J., *Pharmacol. Rev.*, **57**, 411–425 (2005).
- Yamakage M., Namiki A., *Can. J. Anesth.*, **49**, 151–164 (2002).
- Mangoni M. E., Tréboulis A., Leoni A.-L., Couette B., Marger L., Le Quang K., Kupfer E., Cohen-Solal A., Vilar J., Shin H.-S., Escande D., Charpentier F., Nargeot J., Lory P., *Circ. Res.*, **98**, 1422–1430 (2006).
- Ernst M. E., Kelly M. W., *Pharmacotherapy*, **18**, 463–485 (1998).
- Portegies M. C. M., Schmitt R., Kraaij C. J., Braat S. H. J. G., Gassner A., Hagemer F., Pozenel H., Prager G., Viersma J. W., van der Wall E. E., Kleinbloesem C. H., Lie K. I., *J. Cardiovasc. Pharmacol.*, **18**, 746–751 (1991).
- Cremers B., Flesch M., Südkamp M., Böhm M., *J. Cardiovasc. Pharmacol.*, **29**, 692–696 (1997).
- Mullins M. E., Horowitz B. Z., Linden D. H. J., Smith G. W., Norton R. L., Stump J., *JAMA*, **280**, 157–158 (1998).
- SoRelle R., *Circulation*, **98**, 831–832 (1998).
- Kumar P. P., Stotz S. C., Paramashivappa R., Beedle A. M., Zamponi G. W., Rao A. S., *Mol. Pharmacol.*, **61**, 649–658 (2002).
- Schenck H. A., Lenkowski P. W., Choudhury-Mukherjee I., Ko S.-H., Stables J. P., Patel M. K., Brown M. L., *Bioorg. Med. Chem.*, **12**, 979–993 (2004).
- Doddareddy M. R., Jung H. K., Lee J. Y., Lee Y. S., Cho Y. S., Koh H. Y., Pae A. N., *Bioorg. Med. Chem.*, **12**, 1605–1611 (2004).
- Doddareddy M. R., Jung H. K., Cha J. H., Cho Y. S., Koh H. Y., Chang M. H., Pae A. N., *Bioorg. Med. Chem.*, **12**, 1613–1621 (2004).
- Lee Y. S., Lee B. H., Park S. J., Kang S. B., Rhim H., Park J.-Y., Lee J.-H., Jeong S.-W., Lee J. Y., *Bioorg. Med. Chem. Lett.*, **14**, 3379–3384 (2004).
- McCalmont W. F., Heady T. N., Patterson J. R., Lindenmuth M. A., Haverstick D. M., Gray L. S., Macdonald T. L., *Bioorg. Med. Chem. Lett.*, **14**, 3691–3695 (2004).
- Jung H. K., Doddareddy M. R., Cha J. H., Rhim H., Cho Y. S., Koh H. Y., Jung B. Y., Pae A. N., *Bioorg. Med. Chem.*, **12**, 3965–3970 (2004).
- Rhim H., Lee Y. S., Park S. J., Chung B. Y., Lee J. Y., *Bioorg. Med. Chem. Lett.*, **15**, 283–286 (2005).
- McCalmont W. F., Patterson J. R., Lindenmuth M. A., Heady T. N., Haverstick D. M., Gray L. S., Macdonald T. L., *Bioorg. Med. Chem.*, **13**, 3821–3839 (2005).
- Park Se. J., Park Su. J., Lee M. J., Rhim H., Kim Y., Lee J.-H., Chung B. Y., Lee J. Y., *Bioorg. Med. Chem.*, **14**, 3502–3511 (2006).
- Ku I. W., Cho S., Doddareddy M. R., Jang M. S., Keum G., Lee J.-H., Chung B. Y., Kim Y., Rhim H., Kang S. B., *Bioorg. Med. Chem. Lett.*, **16**, 5244–5248 (2006).
- Choi J. Y., Seo H. N., Lee M. J., Park Se. J., Park Su. J., Jeon J. Y., Kang J. H., Pae A. N., Rhim H., Lee J. Y., *Bioorg. Med. Chem. Lett.*, **17**, 471–475 (2007).
- Kim H. S., Kim Y., Doddareddy M. R., Seo S. H., Rhim H., Tae J., Pae A. N., Choo H., Cho Y. S., *Bioorg. Med. Chem. Lett.*, **17**, 476–481 (2007).
- Doddareddy M. R., Choo H., Cho Y. S., Rhim H., Koh H. Y., Lee J.-H., Jeong S.-W., Pae A. N., *Bioorg. Med. Chem.*, **15**, 1091–1105 (2007).
- Park J. H., Choi J. K., Lee E., Lee J. K., Rhim H., Seo S. H., Kim Y., Doddareddy M. R., Pae A. N., Kang J., Roh E. J., *Bioorg. Med. Chem.*, **15**, 1409–1419 (2007).
- Seo H. N., Choi J. Y., Choe Y. J., Kim Y., Rhim H., Lee S. H., Kim J., Joo D. J., Lee J. Y., *Bioorg. Med. Chem. Lett.*, **17**, 5740–5743 (2007).
- Hangeland J. J., Cheney D. L., Friends T. J., Swartz S., Levesque P. C., Rich A. J., Sun L., Bridal T. R., Adam L. P., Normandin D. E., Murugesan N., Ewing W. R., *Bioorg. Med. Chem. Lett.*, **18**, 474–478 (2008).
- Oh Y., Kim Y., Seo S. H., Lee J. K., Rhim H., Pae A. N., Jeong K.-S., Choo H., Cho Y. S., *Bull. Korean Chem. Soc.*, **29**, 1881–1882 (2008).
- Shipe W. D., Barrow J. C., Yang Z.-Q., Lindsley C. W., Yang F. V., Schlegel K.-A. S., Shu Y., Rittle K. E., Bock M. G., Hartman G. D., Tang C., Ballard J. E., Kuo Y., Adarayan E. D., Prueksaritanont T., Zrada M. M., Uebele V. N., Nuss C. E., Connolly T. M., Doran S. M., Fox S. V., Kraus R. L., Marino M. J., Graufelds V. K., Vargas H. M., Bunting P. B., Hasbun-Manning M., Evans R. M., Koblan K. S., Renger J. J., *J. Med. Chem.*, **51**, 3692–3695 (2008).
- Heo J. H., Seo H. N., Choe Y. J., Kim S., Oh C. R., Kim Y. D., Rhim H., Choo D. J., Kim J., Lee J. Y., *Bioorg. Med. Chem. Lett.*, **18**, 3899–3901 (2008).
- Lee H. K., Lee Y. S., Roh E. J., Rhim H., Lee J. Y., Shin K. J., *Bioorg. Med. Chem. Lett.*, **18**, 4424–4427 (2008).
- Yang Z.-Q., Barrow J. C., Shipe W. D., Schlegel K.-A. S., Shu Y., Yang F. V., Lindsley C. W., Rittle K. E., Bock M. G., Hartman G. D., Uebele V. N., Nuss C. E., Fox S. V., Kraus R. L., Doran S. M., Connolly T. M., Tang C., Ballard J. E., Kuo Y., Adarayan E. D., Prueksaritanont T., Zrada M. M., Marino M. J., Graufelds V. K., DiLella A. G., Reynolds I. J., Vargas H. M., Bunting P. B., Woltmann R. F., Magee M. M., Koblan K. S., Renger J. J., *J. Med. Chem.*, **51**, 6471–6477 (2008).
- Jeong J. A., Cho H., Jung S. Y., Kang H. B., Park J. Y., Kim J., Choo D. J., Lee J. Y., *Bioorg. Med. Chem. Lett.*, **20**, 38–41 (2010).
- Gu S. J., Lee J. K., Pae A. N., Chung H. J., Rhim H., Han S. Y., Min S.-J., Cho Y. S., *Bioorg. Med. Chem. Lett.*, **20**, 2705–2708 (2010).
- Lee J. E., Koh H. Y., Seo S. H., Baek Y. Y., Rhim H., Cho Y. S., Choo H., Pae A. N., *Bioorg. Med. Chem. Lett.*, **20**, 4219–4222 (2010).
- Smith E. M., Sorota S., Kim H. M., McKittrick B. A., Nechuta T. L., Bennett C., Knutson C., Burnett D. A., Kieselgoff J., Tan Z., Rindgen D., Bridal T., Zhou X., Jia Y.-P., Dong Z., Mullins D., Zhang X., Priestley T., Correll C. C., Tulshian D., Czarniecki M., Greenlee W. J., *Bioorg. Med. Chem. Lett.*, **20**, 4602–4606 (2010).
- Schlegel K.-A. S., Yang Z.-Q., Reger T. S., Shu Y., Cube R., Rittle K. E., Bondiskey P., Bock M. G., Hartman G. D., Tang C., Ballard J., Kuo Y., Prueksaritanont T., Nuss C. E., Doran S. M., Fox S. V., Garson S. L., Kraus R. L., Li Y., Uebele V. N., Renger J. J., Barrow J. C., *Bioorg. Med. Chem. Lett.*, **20**, 5147–5152 (2010).
- Kam Y. L., Rhee H.-K., Rhim H., Back S. K., Na H. S., Choo H.-Y. P., *Bioorg. Med. Chem.*, **18**, 5938–5944 (2010).
- Fritch P. C., Krajewski J., *Bioorg. Med. Chem. Lett.*, **20**, 6375–6378 (2010).
- Choi Y.-H., Baek J., Seo S. H., Lee J. K., Pae A. N., Cho Y. S., Min S.-J., *Bioorg. Med. Chem. Lett.*, **21**, 215–219 (2011).
- Reger T. S., Yang Z.-Q., Schlegel K.-A. S., Shu Y., Mattern C., Cube R., Rittle K. E., McGaughey G. B., Hartman G. D., Tang C., Ballard J., Kuo Y., Prueksaritanont T., Nuss C. E., Doran S. M., Fox S. V., Garson S. L., Li Y., Kraus R. L., Uebele V. N., Renger J. J., Barrow J. C., *Bioorg. Med. Chem. Lett.*, **21**, 1692–1696 (2011).
- Watanuki S., Matsuura K., Tomura Y., Okada M., Okazaki T., Ohta M., Tsukamoto S., *Chem. Pharm. Bull.*, **59**, 1029–1037 (2011).
- Watanuki S., Matsuura K., Tomura Y., Okada M., Okazaki T., Ohta M., Tsukamoto S., *Bioorg. Med. Chem.*, **19**, 5628–5638 (2011).
- Jirgensons A., Kauss V., Kalvinsh I., Gold M. R., *Synthesis*, **2000**, 1709–1712 (2000).
- Hengartner U., Ramuz H., E. P. Patent, 388739 (1990) [*Chem. Abstr.*, **114**, 732 (1991)].