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# Synthesis and pharmacological evaluation of 1-alkyl-*N*-[2-ethyl-2-(4-fluorophenyl)butyl]piperidine-4-carboxamide derivatives as novel antihypertensive agents

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ABSTRACT

We synthesized and evaluated inhibitory activity against T-type $Ca^{2+}$ channels for a series of 1-alkyl-*N*-[2-ethyl-2-(4-fluorophenyl)butyl]piperidine-4-carboxamide derivatives. Structure–activity relationship studies have revealed that dialkyl substituents at the benzylic position play an important role in increasing inhibitory activity. Oral administration of *N*-[2-ethyl-2-(4-fluorophenyl)butyl]-1-(2-phenylethyl)piperidine-4-carboxamide (**20d**) lowered blood pressure in spontaneously hypertensive rats without inducing reflex tachycardia, which is often caused by traditional L-type $Ca^{2+}$ channel blockers.


## 1. Introduction

Intracellular $Ca^{2+}$ is known to play an important role in various cellular functions, and $Ca^{2+}$ channels on the cell membrane rigorously regulate concentration by influx of $Ca^{2+}$. Voltage-gated calcium channels are located in the nervous, endocrine, cardiovascular, and skeletal systems and are modulated by membrane potential.[1] This series of $Ca^{2+}$ channels is divided into various subtypes based on functional and pharmacological properties: high-voltage-activated channels which can be subdivided into L-, N-, P/Q-, and R-types require a strong depolarization to be activated, whereas low-voltage-activated or T-type (transient) channels are first activated by a relatively weak depolarization and then rapidly inactivated.[2] Of these two subtypes, the T-type-channels are believed to contribute to the regulation of cardiovascular activities such as heart rate (HR), arterial and venous smooth muscle intervention, and tone.[3] As such, these types of channel are regarded as important therapeutic targets for treating various cardiovascular diseases such as hypertension, angina, heart failure, and arrhythmia.

Mibefradil (**1**), the first launched T-type $Ca^{2+}$ channel blocker, demonstrated superior efficacy over the traditional L-type $Ca^{2+}$ channel blockers in treating hypertension and angina, and the adverse effects often seen by the treatment with L-type $Ca^{2+}$ channel blockers were not reported (such as reflex tachycardia, negative inotropy, vasoconstrictive hormone release, and peripheral edema).[4] However, despite its excellent antihypertensive effect, mibefradil was withdrawn from the market in 1998 due to drug–drug interactions.[5] Since then, substantial research efforts have been made in identifying new types of T-type $Ca^{2+}$ channel blockers.[6]

In our research on novel antihypertensive drugs, we previously reported on the utility of novel tetrahydroisoquinoline derivatives.[7] We subsequently conducted high-throughput screening (HTS) using Astellas chemical library to identify a new series of T-type $Ca^{2+}$ channel blockers. On examination of inhibitory activities against T-type $Ca^{2+}$ channels, we identified compound **2** (Fig. 1), which showed moderate inhibitory activity ($IC_{50}$ = 0.32 μM) and a similar bradycardic profile to mibefradil (Table 1).

Here, we describe the synthesis, structure–activity relationship, and pharmacological properties of 1-alkyl-*N*-[2-ethyl-2-(4-fluorophenyl)butyl]piperidine-4-carboxamide derivatives as novel T-type $Ca^{2+}$ channel blocking agents.

## 2. Chemistry

The preparation of 1-benzyl-*N*-{[1-(4-fluorophenyl)cycloalkyl]methyl}piperidinecarboxamide derivatives is outlined in

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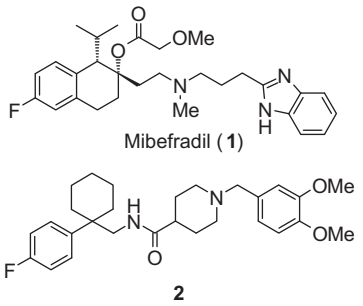



**Figure 1.** Chemical structures of T-type $Ca^{2+}$ channel blocker.

**Table 1**
Pharmacological properties of **1** and **2**

| Compound | T-type[a] $IC_{50}$ (μM) | Bradycardic activity[b] $EC_{30}$ (μM) |
|---|---|---|
| Mibefradil (**1**) | 0.20 | 2.9 |
| **2** | 0.32 | 2.1 |

[a] Inhibition of $Ca^{2+}$ influx through T-type $Ca^{2+}$ channels. See Section 5.2.1.
[b] See Section 5.2.2.

Scheme 1. 4-Fluorophenylacetonitrile **3** was first transformed to carboxamide **4a**–**f** in a three-step sequence consisting of dialkylation of the benzylic position with dibromoalkane, hydrogenation of the nitrile group in the presence of Raney–Ni, and condensation with *tert*-butoxycarbonyl(Boc)-protected piperidinecarboxylic acid in the presence of 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (WSCD) and 1-hydroxybenzotriazole (HOBt). Deprotection of the Boc group by treatment with hydrogen chloride followed by reductive alkylation with benzaldehyde produced 1-benzylpiperidinecarboxamides **5a**–**f**.

Compounds containing functional groups other than the amide moiety were synthesized as shown in Scheme 2. Amine derivative **8** was obtained by reductive alkylation of amine **6** with aldehyde **7**.[8] Ketone derivative **12** was synthesized as follows: 1-(4-fluorophenyl)cyclohexanecarbonitrile **9** was converted into ketone **11** by reduction of the nitrile, Horner–Wadsworth–Emmons reaction of the resulting aldehyde with **10**,[9] and hydrogenation of the double bond. Deprotection followed by reductive alkylation furnished the desired compound **12**. *N*-Methyl derivative **13** was synthesized by methylation of **4a**, deprotection of the Boc group, and reductive alkylation. Compound **18** was prepared as follows: allylation of alcohol **14** with allyltrimethylsilane[10] and dihydroxylation with a catalytic amount of $OsO_4$ and NMO afforded diol **15**. Oxidative cleavage of *vic*-diol followed by Pinnick oxidation gave carboxylic acid **16**. Amidation of **16** with amine **17** using the corresponding acid chloride resulted in the target compound **18**.

Synthesis of **20a**–**s** is depicted in Scheme 3. Nitrile **3** was converted into key intermediate **19a**–**c** by dialkylation of the benzylic position, reduction of the nitrile, and condensation with 1-(Boc)piperidine-4-carboxylic acid. After deprotection of the Boc group, alkylation of the piperidines was carried out via two general methods, A and B. Compounds **20a**–**e**, **20h**–**n**, and **20q**–**s** were synthesized by reductive alkylation with corresponding aldehydes (Method A), and compounds **20f**, **20g**, **20o**, and **20p** were prepared by alkylation with various alkylating agents under basic conditions (Method B).

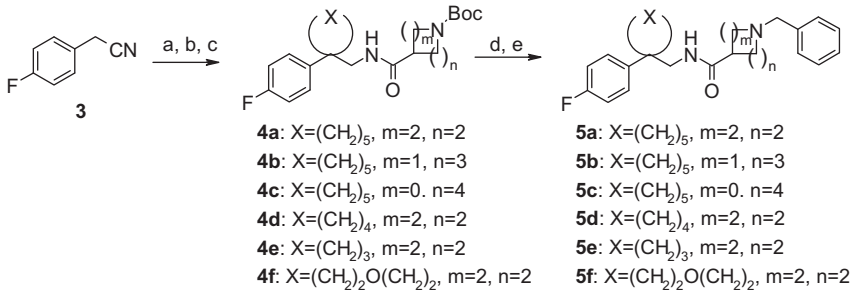
## 3. Results and discussion

In the present study, we first investigated the effect of changing the substitution pattern of the piperidine ring, as shown in Table 2. The parent compound **5a** showed moderate inhibitory activity against T-type $Ca^{2+}$ channels, with an $IC_{50}$ value of 0.51 μM. The 3-piperidyl derivative **5b** exhibited an approximately twofold decrease in activity compared to **5a**, while the 2-piperidyl derivative **5c** was found to be less effective than **5b**. These results indicated that the substitution position on the piperidine ring influences a compound's inhibitory activity against T-type $Ca^{2+}$ channels to some extent.

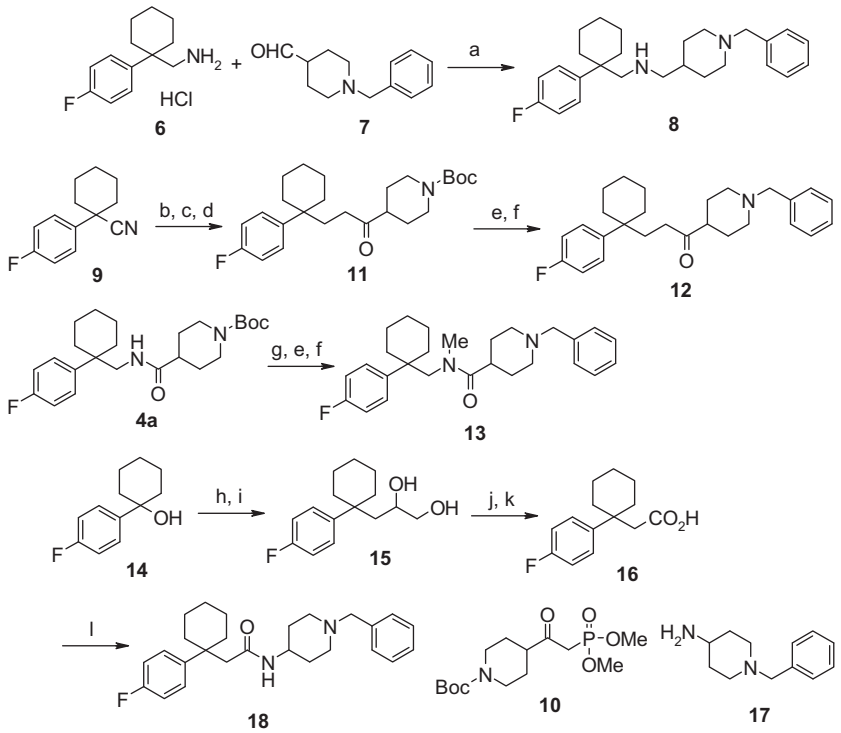
We then examined the tether between the piperidine ring and 1-(4-fluorophenyl)cyclohexyl moiety of compound **5a** (Table 3). Conversion of the amide to a secondary amine (**8**) or ketone (**12**) resulted in two and fourfold decreased activity compared to **5a**, respectively. N-methylated compound **13** and the inverse amide compound **18** were slightly less potent than **5a**. Given these findings, we concluded that amide functionality is the most suitable tether for achieving potent inhibitory activity towards T-type $Ca^{2+}$ channels.

We also examined the effects on cyclohexyl group of applying different alkyl substituents at the benzylic position (Table 4). Cyclopentyl analog **5d** showed twofold improvement in inhibitory activity compared to **5a**, and cyclobutyl analog (**5e**) retained the activity. Tetrahydro-4-pyran analog **5f** was found to be less potent than **5a**. Dimethyl derivative **20a** and diethyl derivative **20b** showed four and sixfold enhancement in inhibitory activity, respectively, while dipropyl derivative **20c** showed only moderate activity. These results indicated that a dialkyl substituent group at the benzylic position plays a crucial role in T-type $Ca^{2+}$ channel inhibitors. In particular, lipophilic substituents of suitable size, such as cyclopentane and a *gem*-diethyl group, are preferable in achieving potent inhibitory activity.

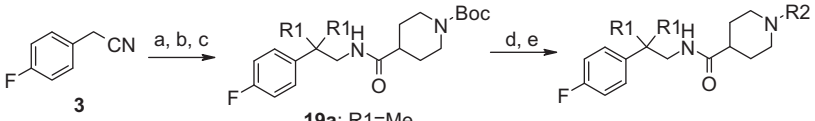
We examined addition of several alkyl groups to the nitrogen atom of the piperidine (Table 5). Phenethyl analog **20d** showed the same level of inhibitory activity as benzyl analog **20b**, with an $IC_{50}$ value of 0.089 μM. Further elongation, such as with the phenylpropyl (**20e**) and phenylbutyl (**20f**) analogs, resulted in decreased activity. Phenoxyethyl analog **20g** exerted inhibitory activity equally potent to that of phenylpropyl analog **20e**. Encouraged by the




**Scheme 1.** Reagents and conditions: (a) Br–X–Br, NaH, DMF; (b) $H_2$, Raney–Ni, $NH_4OH$, EtOH; (c) *N*-(Boc)piperidinecarboxylic acid, WSCD, HOBt, DMF; (d) HCl, AcOEt; (e) benzaldehyde, $NaBH(OAc)_3$, AcONa, $CH_2Cl_2$.




**Scheme 2.** Reagents and conditions: (a) $NaBH(OAc)_3$, AcONa, $CH_2Cl_2$; (b) DIBAL–H, PhMe; (c) **10**, NaH, THF; (d) $H_2$, Pd/C, EtOH; (e) HCl, AcOEt; (f) benzaldehyde, $NaBH(OAc)_3$, AcONa, $CH_2Cl_2$; (g) MeI, NaH, DMF; (h) allyltrimethylsilane, $BF_3{\cdot}OEt_2$, $CH_2Cl_2$; (i) $OsO_4$ (cat), NMO, $H_2O$, $CH_3CN$; (j) $NaIO_4$, $H_2O$, $Et_2O$; (k) $NaClO_2$, $NaH_2PO_4$, 2-methyl-2-butene, *t*BuOH, $H_2O$; (l) $SOCl_2$, DMF (cat), $CH_2Cl_2$ then **17**, $Et_3N$, $CH_2Cl_2$.



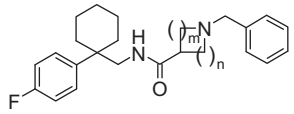

**20a**: R1=Me, R2=$CH_2Ph$
**20b**: R1=Et, R2=$CH_2Ph$
**20c**: R1=Pr, R2=$CH_2Ph$
**20d**: R1=Et, R2=$CH_2CH_2Ph$
**20e**: R1=Et, R2=$CH_2CH_2CH_2Ph$
**20f**: R1=Et, R2=$CH_2CH_2CH_2CH_2Ph$
**20g**: R1=Et, R2=$CH_2CH_2OPh$
**20h**: R1=Et, R2=$CH_2(2\text{-}FC_6H_4)$
**20i**: R1=Et, R2=$CH_2(3\text{-}FC_6H_4)$
**20j**: R1=Et, R2=$CH_2(4\text{-}FC_6H_4)$
**20k**: R1=Et, R2=$CH_2(2\text{-}OMeC_6H_4)$
**20l**: R1=Et, R2=$CH_2(3\text{-}OMeC_6H_4)$
**20m**: R1=Et, R2=$CH_2(4\text{-}OMeC_6H_4)$
**20n**: R1=Et, R2=$CH_2CH_2(2\text{-}FC_6H_4)$
**20o**: R1=Et, R2=$CH_2CH_2(3\text{-}FC_6H_4)$
**20p**: R1=Et, R2=$CH_2CH_2(4\text{-}FC_6H_4)$
**20q**: R1=Et, R2=$CH_2CH_2(2\text{-}OMeC_6H_4)$
**20r**: R1=Et, R2=$CH_2CH_2(3\text{-}OMeC_6H_4)$
**20s**: R1=Et, R2=$CH_2CH_2(4\text{-}OMeC_6H_4)$

**Scheme 3.** Reagents and conditions: (a) R1–I, NaH, DMF; (b) $H_2$, Raney–Ni, $NH_4OH$, EtOH; (c) 1-(Boc)piperidine-4-carboxylic acid, WSCD, HOBt, DMF; (d) HCl, AcOEt; (e) aldehyde, $NaBH(OAc)_3$, $CH_2Cl_2$ (Method A) or alkyl–X (X = Br, OTs), $K_2CO_3$, $CH_3CN$ (Method B).

significant inhibitory activities of the benzyl and phenethyl analogs, we further explored the structure–activity relationship of substituents on the arene ring of **20b** or **20d**, with results shown in Table 6. While introduction of methoxy groups did not improve the inhibitory activity of both series (**20k**–**m**, **20q**–**s**), introduction of a fluorine at the 2-position proved to be quite effective in achieving potent inhibitory activity in both the benzyl and phenethyl series. In particular, 2-fluorobenzyl derivative **20h** was found to be the most potent compound, with an $IC_{50}$ value of 0.036 μM.

Based on these findings, we selected compound **20h** and **20d** for evaluation of bradycardic activities in isolated guinea pig right atria (Table 7). Both were found to exert potent bradycardic activity,

**Table 2**
T-type $Ca^{2+}$ channel blocking activity of 1-benzyl-*N*-{[1-(4-fluorophenyl)cyclohexyl]methyl}piperidinecarboxamide derivatives (**5a–c**)



| Compound | Structure | $IC_{50}$ (μM)[a] |
|---|---|---|
| **5a** | *m* = 2, *n* = 2 | 0.51 |
| **5b** | *m* = 3, *n* = 1 | 1.2 |
| **5c** | *m* = 4, *n* = 0 | 3.0 |

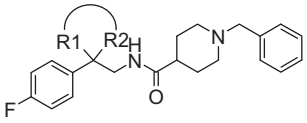
[a] Inhibition of $Ca^{2+}$ influx through T-type $Ca^{2+}$ channels. See Section 5.2.1.

**Table 3**
T-type $Ca^{2+}$ channel blocking activity of piperidine derivatives (**5a**, **8**, **12**, **13**, **18**)

| Compound | $IC_{50}$[a] (μM) |
|---|---|
| **5a** | 0.51 |
| **8** | 1.2 |
| **12** | 2.0 |
| **13** | 0.75 |
| **18** | 0.86 |

[a] Inhibition of $Ca^{2+}$ influx through T-type $Ca^{2+}$ channels. See Section 5.2.1.

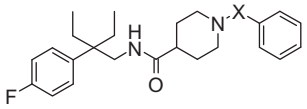
**Table 4**
T-type $Ca^{2+}$ channel blocking activity of 1-benzylpiperidine-4-carboxamide derivatives (**5a**, **5d–f**, **20a–c**)



| Compound | Structure | $IC_{50}$[a] (μM) |
|---|---|---|
| **5a** | R1, R2 = $(CH_2)_5$ | 0.51 |
| **5d** | R1, R2 = $(CH_2)_4$ | 0.22 |
| **5e** | R1, R2 = $(CH_2)_3$ | 0.39 |
| **5f** | R1, R2 = $(CH_2)_2O(CH_2)_2$ | 2.2 |
| **20a** | R1 = Me, R2 = Me | 0.13 |
| **20b** | R1 = Et, R2 = Et | 0.085 |
| **20c** | R1 = Pr, R2 = Pr | 0.37 |

[a] Inhibition of $Ca^{2+}$ influx through T-type $Ca^{2+}$ channels. See Section 5.2.1.

**Table 5**
T-type $Ca^{2+}$ channel blocking activity of 1-alkyl-*N*-[2-ethyl-2-(4-fluorophenyl)butyl]piperidine-4-carboxamide derivatives (**20b**, **20d–g**)

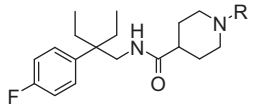


| Compound | Structure | $IC_{50}$[a] (μM) |
|---|---|---|
| **20b** | X = $CH_2$ | 0.085 |
| **20d** | X = $CH_2CH_2$ | 0.089 |
| **20e** | X = $CH_2CH_2CH_2$ | 0.24 |
| **20f** | X = $CH_2CH_2CH_2CH_2$ | 0.25 |
| **20g** | X = $CH_2CH_2O$ | 0.26 |

[a] Inhibition of $Ca^{2+}$ influx through T-type $Ca^{2+}$ channels. See Section 5.2.1.

with respective $ED_{30}$ values of 4.2 and 2.5 μM. Interestingly, the $ED_{30}$ value of compound **20d** was found to be comparable to the value of mibefradil (2.9 μM).

**Table 6**
T-type $Ca^{2+}$ channel blocking activity of 1-alkyl-*N*-[2-ethyl-2-(4-fluorophenyl)butyl]piperidine-4-carboxamide derivatives (**20b**, **20d**, **20h–s**)



| Compound | Structure | $IC_{50}$[a] (μM) |
|---|---|---|
| **20b** | R = $CH_2Ph$ | 0.085 |
| **20d** | R = $CH_2CH_2Ph$ | 0.089 |
| **20h** | R = $CH_2(2\text{-}FC_6H_4)$ | 0.036 |
| **20i** | R = $CH_2(3\text{-}FC_6H_4)$ | 0.13 |
| **20j** | R = $CH_2(4\text{-}FC_6H_4)$ | 0.082 |
| **20k** | R = $CH_2(2\text{-}OMeC_6H_4)$ | 0.12 |
| **20l** | R = $CH_2(3\text{-}OMeC_6H_4)$ | 0.094 |
| **20m** | R = $CH_2(4\text{-}OMeC_6H_4)$ | 0.20 |
| **20n** | R = $CH_2CH_2(2\text{-}FC_6H_4)$ | 0.090 |
| **20o** | R = $CH_2CH_2(3\text{-}FC_6H_4)$ | 0.13 |
| **20p** | R = $CH_2CH_2(4\text{-}FC_6H_4)$ | 0.18 |
| **20q** | R = $CH_2CH_2(2\text{-}OMeC_6H_4)$ | 0.17 |
| **20r** | R = $CH_2CH_2(3\text{-}OMeC_6H_4)$ | 0.14 |
| **20s** | R = $CH_2CH_2(4\text{-}OMeC_6H_4)$ | 0.77 |

[a] Inhibition of $Ca^{2+}$ influx through T-type $Ca^{2+}$ channels. See Section 5.2.1.

**Table 7**
Pharmacological properties of selected compound (**20h**, **20d**, **1**)

| Compound | T-type[a] $IC_{50}$ (μM) | Bradycardic activity[b] $EC_{30}$ (μM) |
|---|---|---|
| **20h** | 0.036 | 4.2 |
| **20d** | 0.089 | 2.5 |
| Mibefradil (**1**) | 0.20 | 2.9 |

[a] Inhibition of $Ca^{2+}$ influx through T-type $Ca^{2+}$ channels. See Section 5.2.1.
[b] See Section 5.2.2.

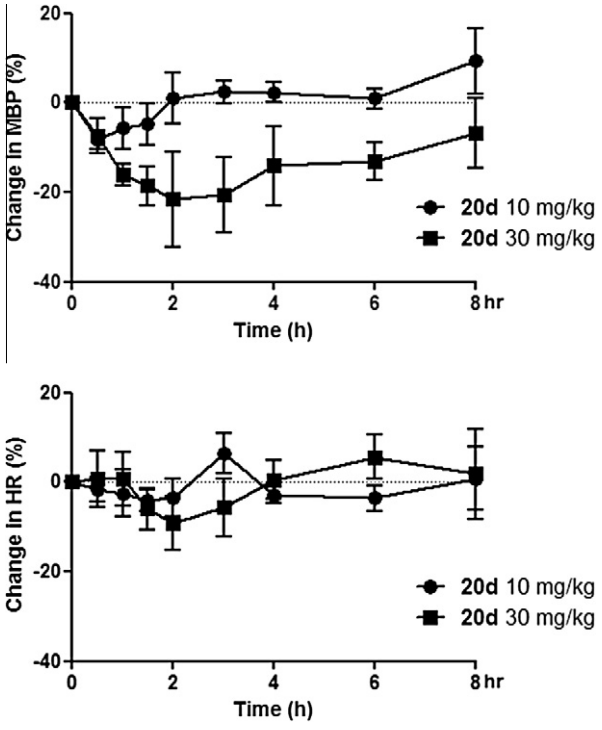



**Figure 2.** Effect of **20d** on mean blood pressure (MBP) and heart rate (HR) in conscious spontaneously hypertensive rats. Compounds were orally administrated at 0 h. The values are mean ± standard error of means from at least three experiments.

Given its potent inhibitory activity against T-type $Ca^{2+}$ channels and the bradycardic activity displayed in isolated guinea pig right atria, **20d** was submitted for further pharmacological evaluations. Oral administration of the compound to spontaneously hypertensive rats induced a dose-dependent reduction of 22% in mean blood pressure at 30 mg/kg po (Fig. 2), and effect which was sustained for more than 8 h. Further, we observed no undesirable reflex tachycardia despite the compound's hypotensive effect. Taken together, these finding strongly support the usefulness of T-type $Ca^{2+}$ channel blockers in treating hypertension.

## 4. Conclusion

A series of 1-alkyl-*N*-[2-ethyl-2-(4-fluorophenyl)butyl]piperidine-4-carboxamide were synthesized and evaluated. Structure–activity relationship studies of this novel class of compounds revealed that benzylic dialkyl substituents played an important role for a potent inhibitory activity against T-type $Ca^{2+}$ channels. Of this series, *N*-[2-ethyl-2-(4-fluorophenyl)butyl]-1-(2-phenylethyl) piperidine-4-carboxamide (**20d**) exerted an antihypertensive effect without undesirable reflex tachycardia when orally administered to spontaneously hypertensive rats. Further research to identify novel antihypertensive agents superior in efficacy to currently available agents is underway and will be reported in due course.

## 5. Experimental

### 5.1. Chemistry

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

#### 5.1.1. *tert*-Butyl 4-({[1-(4-fluorophenyl)cyclohexyl]methyl} carbamoyl)piperidine-1-carboxylate (4a)

To an ice-cooled solution of 4-fluorophenylacetonitrile (**3**, 5.0 g, 37.0 mmol) and 1,5-dibromopentane (5.4 ml, 39.9 mmol) in DMF (50 ml) was added potionwise 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 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 = 1/20) to give 1-(4-fluorophenyl)cyclohexanecarbonitrile (5.49 g, 73%) as a colorless oil. To a suspension of Raney–Ni (ca 2.0 g) and 28 w/w% $NH_4OH$ (1.5 ml) in EtOH (15 ml) was added the nitrile obtained above (4.45 g, 21.9 mmol) and the mixture was stirred under hydrogen atmosphere at room temperature for 23 h. The catalyst was removed by filtration and the filtrate was concentrated in vacuo to give 1-[1-(4-fluorophenyl)cyclohexyl]methylamine (4.5 g, quantitative) as a light yellow oil. To an ice-cooled mixture of the amine obtained above (4.5 g, 21.9 mmol), 1-(Boc)piperidine-4-carboxylic acid (5.2 g, 22.7 mmol), and HOBt (3.1 g, 22.9 mmol) in DMF (10 ml) was added WSCD (4.4 g, 23.0 mmol) and the mixture was stirred at room temperature for 26 h. 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 = 1/1) to give the title compound **4a** (8.86 g, 97%) as a light yellow foam.

$^1$H NMR ($CDCl_3$) $\delta$: 1.30–1.70 (21H, m), 1.95–2.12 (3H, m), 2.62–2.75 (2H, m), 3.37 (2H, d, $J$ = 6.0 Hz), 4.09 (2H, br s), 4.94 (1H, br s), 7.07 (2H, dd, $J$ = 8.4, 8.4 Hz), 7.30 (2H, dd, $J$ = 5.2, 8.4 Hz). MS (FAB) $m/z$: 419 ($M^+$+1).

#### 5.1.2. *tert*-Butyl 3-({[1-(4-fluorophenyl)cyclohexyl]methyl} carbamoyl)piperidine-1-carboxylate (4b)

The title compound was prepared in the same manner as described for **4a** using 1-(Boc)piperidine-3-carboxylic acid instead of 1-(Boc)piperidine-4-carboxylic acid, in 83% yield.

$^1$H NMR ($CDCl_3$) $\delta$: 1.30–1.76 (21H, m), 1.97–2.12 (3H, m), 2.81 (1H, t, $J$ = 12.4 Hz), 2.95 (1H, dd, $J$ = 10.0, 13.6 Hz), 3.30 (1H, dd, $J$ = 6.0, 13.6 Hz), 3.40 (1H, dd, $J$ = 6.4, 13.6 Hz), 3.78–3.95 (2H, m), 5.23 (1H, br s), 7.06 (2H, dd, $J$ = 8.4, 8.8 Hz), 7.30 (2H, dd, $J$ = 5.6, 8.8 Hz). MS (ESI) $m/z$: 419 ($M^+$+1).

#### 5.1.3. *tert*-Butyl 2-({[1-(4-fluorophenyl)cyclohexyl]methyl} carbamoyl)piperidine-1-carboxylate (4c)

The title compound was prepared in the same manner as described for **4a** using 1-(Boc)piperidine-2-carboxylic acid instead of 1-(Boc)piperidine-4-carboxylic acid, in quantitative yield.

$^1$H NMR ($CDCl_3$) $\delta$: 1.30–1.68 (22H, m), 1.97–2.07 (2H, m), 2.19–2.28 (1H, m), 2.49 (1H, br s), 3.31 (1H, dd, $J$ = 5.2, 13.6 Hz), 3.44 (1H, dd, $J$ = 6.8, 13.6 Hz), 3.38 (1H, br s), 4.62 (1H, br s), 5.64 (1H, br s), 7.03 (2H, dd, $J$ = 8.4, 8.8 Hz), 7.29 (2H, dd, $J$ = 5.6, 8.8 Hz). MS (ESI) $m/z$: 419 ($M^+$+1).

#### 5.1.4. *tert*-Butyl 4-({[1-(4-fluorophenyl)cyclopentyl]methyl} carbamoyl)piperidine-1-carboxylate (4d)

The title compound was prepared in the same manner as described for **4a** using 1,4-dibromobutane instead of 1,5-dibromopropane, in 90% yield.

$^1$H NMR ($CDCl_3$) $\delta$: 1.40–1.95 (21H, m), 2.04–2.12 (1H, m), 2.62–2.77 (2H, m), 3.38 (2H, d, $J$ = 6.4 Hz), 4.09 (2H, br s), 5.04 (1H, br s), 7.03 (2H, dd, $J$ = 8.4, 8.4 Hz), 7.30 (2H, dd, $J$ = 5.2, 8.4 Hz). MS (FAB) $m/z$: 405 ($M^+$+1).

#### 5.1.5. *tert*-Butyl 4-({[1-(4-fluorophenyl)cyclobutyl]methyl} carbamoyl)piperidine-1-carboxylate (4e)

The title compound was prepared in the same manner as described for **4a** using 1,3-dibromopropane instead of 1,5-dibromopropane, in 53% yield.

$^1$H NMR ($CDCl_3$) $\delta$: 1.45 (9H. s), 1.45–1.62 (2H, m), 1.67–1.74 (2H, m), 1.85–1.92 (1H, m), 2.05–2.33 (6H, m), 2.64–2.77 (2H, m), 3.60 (2H, d, $J$ = 6.4 Hz), 4.10 (2H, br s), 5.10 (1H, br s), 7.00–7.11 (4H, m). MS (FAB) $m/z$: 391 ($M^+$+1).

#### 5.1.6. *tert*-Butyl 4-({[4-(4-fluorophenyl)tetrahydro-2*H*-pyran-4-yl]methyl}carbamoyl)piperidine-1-carboxylate (4f)

The title compound was prepared in the same manner as described for **4a** using bis(2-bromoethyl) ether instead of 1,5-dibromopropane, in 89% yield.

$^1$H NMR ($CDCl_3$) $\delta$: 1.45 (9H, s), 1.45–1.55 (2H, m), 1.63–1.70 (2H, m), 1.82–1.90 (2H, m), 1.98–2.12 (3H, m), 2.60–2.75 (2H, m), 3.49 (2H, d, $J$ = 6.4 Hz), 3.55–3.64 (2H, m), 3.79–3.87 (2H, m), 4.10 (2H, br s), 4.99 (1H, br s), 7.10 (2H, dd, $J$ = 8.4, 8.4 Hz), 7.26 (2H, dd, $J$ = 5.2, 8.4 Hz). MS (FAB) $m/z$: 421 ($M^+$+1).

#### 5.1.7. 1-Benzyl-*N*-{[1-(4-fluorophenyl)cyclohexyl]methyl} piperidine-4-carboxamide hydrochloride (5a)

To an ice-cooled solution of **4a** (2.05 g, 4.90 mmol) in AcOEt (5.0 ml) was added 4 M HCl–AcOEt (10 ml, 40.0 mmol), and the mixture was stirred at room temperature for 18 h. After

concentration of the reaction mixture, the resulting solid was suspended with AcOEt and collected by filtration to give *N*-{[1-(4-fluorophenyl)cyclohexyl]methyl}piperidine-4-carboxamide hydrochloride (1.46 g, 84%) as a light yellow solid. To an ice-cooled mixture of the piperidine derivative obtained above (0.30 g, 845 μmol), benzaldehyde (0.10 ml, 984 μmol), and sodium acetate (0.10 g, 1.22 mmol) in $CH_2Cl_2$ (5.0 ml) was added sodium triacetoxyborohydride (0.22 g, 1.04 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 1-benzyl-*N*-{[1-(4-fluorophenyl)cyclohexyl]methyl}piperidine-4-carboxamide (0.26 g) as a yellow oil. The compound was converted to its hydrochloride salt by treating it with 4 M HCl–AcOEt (0.20 ml, 800 μmol). The crude salt was suspended with AcOEt and filtered to give the title compound **5a** (0.26 g, 71%) as a colorless powder.

$^1$H NMR (DMSO-$d_6$) $\delta$: 1.15–2.06 (14H, m), 2.25–2.35 (1H, m), 2.73–2.98 (2H, m), 3.11 (2H, d, $J$ = 6.4 Hz), 3.19–3.33 (2H, m), 4.20–4.27 (2H, m), 7.10 (2H, dd, $J$ = 8.4, 8.8 Hz), 7.32 (2H, dd, $J$ = 5.4, 8.8 Hz), 7.42–7.48 (3H, m), 7.54 (1H, t, $J$ = 6.4 Hz), 7.55–7.62 (2H, m), 10.37 and 10.75 (1H, br s). MS (FAB) *m/z*: 409 ($M^+$+1). Anal. Calcd for $C_{26}H_{33}N_2OF{\cdot}HCl{\cdot}0.3H_2O$: C, 69.33; H, 7.74; N, 6.22; Cl, 7.87; F, 4.33. Found: C, 69.44; H, 7.54; N, 5.93; Cl, 7.73; F, 4.15.

### 5.1.8. 1-Benzyl-*N*-{[1-(4-fluorophenyl)cyclohexyl]methyl} piperidine-3-carboxamide hydrochloride (5b)

The title compound was prepared in the same manner as described for **5a** using **4b** instead of **4a**, in 18% yield.

$^1$H NMR (DMSO-$d_6$) $\delta$: 1.10–2.08 (15H, m), 2.65–3.11 (6H, m), 4.20–4.30 (2H, m), 7.07 (2H, dd, $J$ = 8.4, 8.8 Hz), 7.30 (2H, dd, $J$ = 5.4, 8.8 Hz), 7.42–7.48 (3H, m), 7.50–7.60 (2H, m), 7.79 and 7.96 (1H, t, $J$ = 6.2 Hz), 8.98 and 10.55 (1H, br s). MS (FAB) *m/z*: 409 ($M^+$+1). Anal. Calcd for $C_{26}H_{33}N_2OF{\cdot}HCl{\cdot}H_2O$: C, 67.44; H, 7.84; N, 6.05; Cl, 7.66; F, 4.10. Found: C, 67.21; H, 7.68; N, 5.84; Cl, 7.54; F, 4.13.

### 5.1.9. 1-Benzyl-*N*-{[1-(4-fluorophenyl)cyclohexyl]methyl} piperidine-2-carboxamide hydrochloride (5c)

The title compound was prepared in the same manner as described for **5a** using **4c** instead of **4a**, in 60% yield.

$^1$H NMR (DMSO-$d_6$) $\delta$: 1.16–1.74 (13H, m), 1.85–1.96 (1H, m), 2.02–2.17 (2H, m), 2.76–2.92 (1H, m), 3.05–3.15 (1H, m), 3.33–3.42 (2H, m), 3.67–3.90 (3H, m), 7.06 (2H, dd, $J$ = 8.4, 8.8 Hz), 7.31–7.37 (2H, m), 7.38–7.47 (5H, m), 7.97 and 8.62 (1H, t, $J$ = 5.9 Hz), 9.73 (1H, br s). MS (FAB) *m/z*: 409 ($M^+$+1). Anal. Calcd for $C_{26}H_{33}N_2OF{\cdot}HCl$: C, 70.17; H, 7.70; N, 6.29; Cl, 7.97; F, 4.27. Found: C, 70.19; H, 7.70; N, 6.16; Cl, 7.99; F, 4.42.

### 5.1.10. 1-Benzyl-*N*-{[1-(4-fluorophenyl)cyclopentyl]methyl} piperidine-4-carboxamide hydrochloride (5d)

The title compound was prepared in the same manner as described for **5a** using **4d** instead of **4a**, in 47% yield.

$^1$H NMR (DMSO-$d_6$) $\delta$: 1.50–1.97 (12H, m), 2.24–2.35 (1H, m), 2.75–2.98 (2H, m), 3.18 (2H, d, $J$ = 6.4 Hz), 3.25–3.33 (2H, m), 4.20–4.27 (2H, m), 7.07 (2H, dd, $J$ = 8.4, 8.8 Hz), 7.25 (2H, dd, $J$ = 5.9, 8.8 Hz), 7.42–7.48 (3H, m), 7.53–7.66 (3H, m), 10.52 and 10.88 (1H, br s). MS (FAB) *m/z*: 395 ($M^+$+1). Anal. Calcd for $C_{25}H_{31}N_2OF{\cdot}HCl$: C, 69.67; H, 7.48; N, 6.50; Cl, 8.23; F, 4.41. Found: C, 69.65; H, 7.53; N, 6.34; Cl, 8.09; F; 4.28.

### 5.1.11. 1-Benzyl-*N*-{[1-(4-fluorophenyl)cyclobutyl]methyl} piperidine-4-carboxamide hydrochloride (5e)

The title compound was prepared in the same manner as described for **5a** using **4e** instead of **4a**, in 86% yield.

$^1$H NMR (DMSO-$d_6$) $\delta$: 1.68–2.26 (10H, m), 2.27–2.37 (1H, m), 2.76–2.98 (2H, m), 3.26–3.42 (4H, m), 4.20–4.30 (2H, m), 7.05–7.13 (4H, m), 7.42–7.48 (3H, m), 7.54–7.62 (2H, m), 7.84 (1H, t, $J$ = 5.9 Hz), 10.28 and 10.67 (1H, br s). MS (FAB) *m/z*: 381 ($M^+$+1). Anal. Calcd for $C_{24}H_{29}N_2OF{\cdot}HCl{\cdot}0.2H_2O$: C, 68.54; H, 7.29; N, 6.66; Cl, 8.43; F, 4.52. Found: C, 68.53; H, 7.38; N, 6.50; Cl, 8.23; F, 4.27.

### 5.1.12. 1-Benzyl-*N*-{[4-(4-fluorophenyl)tetrahydro-2*H*-pyran-4-yl]methyl}piperidine-4-carboxamide hydrochloride (5f)

The title compound was prepared in the same manner as described for **5a** using **4f** instead of **4a**, in 42% yield.

$^1$H NMR (DMSO-$d_6$) $\delta$: 1.68–2.02 (8H, m), 2.25–2.35 (1H, m), 2.76–2.90 (2H, m), 3.20–3.40 (6H, m), 3.64–3.74 (2H, m), 4.20–4.28 (2H, m), 7.13 (2H, dd, $J$ = 8.4, 8.7 Hz), 7.33 (2H, dd, $J$ = 5.3, 8.7 Hz) 7.42–7.48 (3H, m), 7.56–7.71 (3H, m), 10.56 and 10.93 (1H, br s). MS (FAB) *m/z*: 411 ($M^+$+1). Anal. Calcd for $C_{25}H_{31}N_2O_2F{\cdot}HCl$: C, 67.18; H, 7.22; N, 6.27; Cl, 7.93; F, 4.25. Found: C, 66.88; H, 7.17; N, 5.82; Cl, 8.02; F, 4.22.

### 5.1.13. 1-(1-Benzylpiperidin-4-yl)-*N*-{[1-(4-fluorophenyl) cyclohexyl]methyl}methanamine dihydrochloride (8)

To an ice-cooled mixture of **6** (0.45 g, 1.85 mmol), **7**[8] (0.45 g, 2.22 mmol), and sodium acetate (0.17 g, 2.03 mmol) in $CH_2Cl_2$ (10 ml) was added sodium triacetoxyborohydride (0.78 g, 3.96 mmol) and the mixture was stirred at room temperature for 20 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 (AcOEt/$CHCl_3$ = 1/1) to give 1-(1-benzylpiperidin-4-yl)-*N*-{[1-(4-fluorophenyl)cyclohexyl]methyl}methanamine (0.80 g) as a yellow solid. The compound was converted to its hydrochloride salt by treating it with 4 M HCl–AcOEt (1.4 ml, 5.20 mmol). The crude salt was suspended with AcOEt and filtered to give the title compound **8** (0.72 g, 85%) as a colorless powder.

$^1$H NMR (DMSO-$d_6$) $\delta$: 1.14–1.60 (8H, m), 1.67–1.82 (4H, m), 1.94 (1H, br s), 2.15–2.23 (2H, m), 2.56–2.64 (2H, m), 2.72–2.87 (2H, m), 2.97–3.07 (2H, m), 3.24–3.35 (2H, m), 4.20–4.28 (2H, m), 7.22 (2H, dd, $J$ = 8.4, 8.7 Hz), 7.42–7.52 (5H, m), 7.58–7.65 (2H, m), 8.25–8.43 (2H, m), 10.95 (1H, br s). MS (FAB) *m/z*: 395 ($M^+$+1). Anal. Calcd for $C_{26}H_{35}N_2F{\cdot}2HCl{\cdot}1.1H_2O$: C, 64.08; H, 8.11; N, 5.75; Cl, 14.55; F, 3.90. Found: C, 64.01; H, 8.11; N, 5.56; Cl, 14.48; F, 3.93.

### 5.1.14. *tert*-Butyl 4-{3-[1-(4-fluorophenyl)cyclohexyl] propanoyl}piperidine-1-carboxylate (11)

To an ice-cooled solution of **9** (1.5 g, 7.38 mmol) in toluene (10 ml) was added dropwise DIBAL–H (1.01 M in toluene; 9.0 ml, 9.09 mmol) and the mixture was stirred at 0 °C for 24 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. The resulting residue was purified by column chromatography on silica gel (AcOEt/hexane = 1/50) to give 1-(4-fluorophenyl)cyclohexanecarbaldehyde (1.42 g, 93%) as a colorless oil. To an ice-cooled solution of *tert*-butyl 4-[(dimethoxyphosphoryl)acetyl]piperidine-1-carboxylate[9] (**10**, 1.28 g, 3.82 mmol) in THF (10 ml) was added potionwise NaH (60% dispersion in mineral oil; 0.50 g, 12.5 mmol) and the mixture was stirred at 0 °C for 10 min.

To this ice-cooled mixture was added the aldehyde obtained above (0.73 g, 3.54 mmol) and the mixture was stirred at room temperature for two days. The reaction mixture was concentrated in vacuo and 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 = 1/8) to give *tert*-butyl 4-{(2*E*)-3-[1-(4-fluorophenyl)cyclohexyl]prop-2-enoyl}piperidine-1-carboxylate (1.10 g, 75%) as a colorless oil. To a solution of the ketone obtained above (0.50 g, 1.20 mmol) in EtOH (10 ml) was added 10% Pd/C (10 w/w%; 0.10 g) and the mixture was stirred under hydrogen atmosphere at room temperature for 20 h. The catalyst was removed by filtration and the filtrate was concentrated in vacuo to give the title compound **11** (0.52 g, quantitative) as a colorless oil.

$^1$H NMR ($CDCl_3$) $\delta$: 1.30–1.65 (21H, m), 1.75–1.81 (2H, m), 1.82–1.90 (2H, m), 1.96–2.10 (2H, m), 2.20–2.33 (1H, m), 2.60–2.75 (2H, m), 3.96–4.09 (2H, m), 7.00 (2H, dd, $J$ = 8.4, 8.4 Hz), 7.25 (2H, dd, $J$ = 5.4, 8.4 Hz). MS (FAB) *m/z*: 418 ($M^+$+1).

### 5.1.15. 1-(1-Benzylpiperidin-4-yl)-3-[1-(4-fluorophenyl) cyclohexyl]propan-1-one fumarate (12)

The title compound was prepared in the same manner as described for **5a** using **11** instead of **4a**, in 42% yield.

$^1$H NMR (DMSO-$d_6$) $\delta$: 1.17–1.69 (14H, m), 1.96–2.08 (6H, m), 2.18–2.29 (1H, m), 2.76–2.86 (2H, m), 3.54 (2H, s), 6.61 (2H, s), 7.12 (2H, dd, $J$ = 8.4, 8.7 Hz), 7.23–7.36 (7H, m). MS (ESI) *m/z*: 408 ($M^+$+1). Anal. Calcd for $C_{27}H_{34}NOF{\cdot}C_4H_4O_4$: C, 71.11; H, 7.31; N, 2.67; F, 3.63. Found: C, 70.85; H, 7.33; N, 2.75; F, 3.62.

### 5.1.16. 1-Benzyl-*N*-{[1-(4-fluorophenyl)cyclohexyl]methyl}-*N*-methylpiperidine-4-carboxamide oxalate (13)

To an ice-cooled solution of **4a** (0.50 g, 1.19 mmol) in DMF (10 ml) was added potionwise NaH (60% dispersion in mineral oil; 60 mg, 1.50 mmol) and the mixture was stirred at 0 °C for 1 h. To this ice-cooled mixture was added iodomethane (0.25 g, 1.76 mmol) and the mixture was stirred at 0 °C for two days. The reaction mixture was concentrated in vacuo and 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 = 2/3) to give *tert*-butyl 4-[{[1-(4-fluorophenyl)cyclohexyl] methyl}(methyl)carbamoyl]piperidine-1-carboxylate (0.51 g, 99%) as a colorless foam. The title compound was prepared in the same manner as described for **5a** using *tert*-butyl 4-[{[1-(4-fluorophenyl)cyclohexyl]methyl}(methyl)carbamoyl]piperidine-1-carboxylate instead of **4a**, in 75% yield.

$^1$H NMR (DMSO-$d_6$, 80 °C) $\delta$: 1.13–1.77 (14H, m), 2.00–2.15 (1H, m), 2.20–2.70 (5H, m), 3.14 (2H, br s), 3.35 (2H, s), 3.88–4.04 (2H, br s), 7.10 (2H, dd, $J$ = 8.4, 8.8 Hz), 7.30–7.44 (7H, m). MS (FAB) *m/z*: 423 ($M^+$+1). Anal. Calcd for $C_{27}H_{35}N_2OF{\cdot}C_2H_2O_2{\cdot}1.4H_2O$: C, 64.76; H, 7.46; N, 5.21; F, 3.53. Found: C, 64.52; H, 7.06; N, 4.87; F, 3.40.

### 5.1.17. 3-[1-(4-Fluorophenyl)cyclohexyl]propane-1,2-diol (15)

To an ice-cooled solution of **14** (0.50 g, 2.57 mmol) and allyltrimethylsilane (0.50 ml, 3.15 mmol) in $CH_2Cl_2$ (5.0 ml) was added $BF_3{\cdot}OEt_2$ (0.40 ml, 3.18 mmol) and the mixture was stirred at room temperature for 15 h. The reaction mixture was concentrated in vacuo and partitioned between $H_2O$ and AcOEt. The organic layer was washed successively with saturated aqueous sodium bicarbonate solution and brine, dried over $Na_2SO_4$, and evaporated in vacuo to give 1-(1-allylcyclohexyl)-4-fluorobenzene (0.52 g, 93%) as a light yellow oil. To a solution of the olefin obtained above (0.52 g, 2.38 mmol), NMO (0.40 g, 3.40 mmol), and $H_2O$ (2.0 ml) in $CH_3CN$ (5.0 ml) was added $OsO_4$ (2.5 w/w% in *t*BuOH; 1.0 ml, ca 100 μmol) and the mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated in vacuo and 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 = 2/3) to give the title compound (0.39 g, 64%) as a orange oil.

$^1$H NMR ($CDCl_3$) $\delta$: 1.30–1.73 (10H, m), 2.06–2.14 (1H, m), 2.15–2.23 (1H, m), 3.19–3.32 (2H, m), 3.50–3.56 (1H, m), 7.04 (2H, dd, $J$ = 8.4, 8.8 Hz), 7.34 (2H, dd, $J$ = 5.2, 8.8 Hz). MS (FAB) *m/z*: 253 ($M^+$+1).

### 5.1.18. [1-(4-Fluorophenyl)cyclohexyl]acetic acid (16)

To an ice-cooled solution of **15** (0.39 g, 1.55 mmol) and $H_2O$ (5.0 ml) in $Et_2O$ (10 ml) was added $NaIO_4$ (0.40 g, 1.87 mmol) and the mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated in vacuo and partitioned between $H_2O$ and AcOEt. The organic layer was washed with brine, dried over $Na_2SO_4$, and evaporated in vacuo to give [1-(4-fluorophenyl)cyclohexyl]acetaldehyde (0.32 g, 94%) as a light yellow oil, which was used for the next step without further purification. To an ice-cooled mixture of the aldehyde obtained above (0.32 g, 1.45 mmol), $NaH_2PO_4{\cdot}2H_2O$ (0.50 g, 3.20 mmol), 2-methyl-2-butene (0.50 ml, 4.71 mmol), and $H_2O$ (2.0 ml) in *t*BuOH (10 ml) was added $NaClO_2$ (80%; 0.25 g, 2.21 mmol) and the mixture was stirred at room temperature for 18 h. The reaction mixture was concentrated in vacuo and 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 (0.39 g, quantitative) as a colorless oil.

$^1$H NMR ($CDCl_3$) $\delta$: 1.30–1.62 (6H, m), 1.71–1.84 (2H, m), 2.12–2.22 (2H, m), 2.52 (2H, s), 7.00 (2H, dd, $J$ = 8.4, 8.8 Hz), 7.31 (2H, dd, $J$ = 5.2, 8.8 Hz). MS (FAB) *m/z*: 235 ($M^+$−1).

### 5.1.19. *N*-(1-Benzylpiperidin-4-yl)-2-[1-(4-fluorophenyl) cyclohexyl]acetamide oxalate (18)

To an ice-cooled solution of **16** (0.39 g, 1.65 mmol) and DMF (1 drop) in PhH (10 ml) was added $SOCl_2$ (0.50 ml, 6.85 mmol) and the mixture was stirred at room temperature for 3 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 **17** (0.40 g, 2.10 mmol) and $Et_3N$ (0.60 ml, 4.30 mmol) in $CH_2Cl_2$ (5.0 ml) was added a solution of the acid chloride obtained above and $CH_2Cl_2$ (10 ml) and the mixture was stirred at room temperature for 18 h. The reaction mixture was concentrated in vacuo and partitioned between $H_2O$ and $CHCl_3$. 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 (MeOH/$CHCl_3$ = 3/97) to give *N*-(1-benzylpiperidin-4-yl)-2-[1-(4-fluorophenyl)cyclohexyl]acetamide (0.47 g) as a yellow foam. The compound was converted to its oxalate by treating it with oxalic acid (0.10 g, 1.11 mmol). The crude salt was suspended with AcOEt and filtered to give the title compound **18** (0.46 g, 56%) as a colorless powder.

$^1$H NMR (DMSO-$d_6$) $\delta$: 1.20–1.43 (6H, m), 1.45–1.55 (2H, m), 1.57–1.66 (2H, m), 1.69–1.80 (2H, m), 2.04–2.14 (2H, m), 2.23 (2H, s), 2.65–2.80 (2H, m), 2.95–3.10 (2H, m), 3.46–3.58 (1H, m), 4.06 (2H, s), 7.06 (2H, dd, $J$ = 8.4, 8.8 Hz), 7.34 (2H, dd, $J$ = 5.3, 8.8 Hz), 7.43 (5H, s), 7.47 (1H, d, $J$ = 7.8 Hz). MS (FAB) *m/z*: 409 ($M^+$+1). Anal. Calcd for $C_{26}H_{33}N_2OF{\cdot}C_2H_2O_2{\cdot}0.5H_2O{\cdot}0.5AcOEt$: C, 65.32; H, 7.31; N, 5.08; F, 3.44. Found: C, 65.48; H, 7.18; N, 5.07; F, 3.52.

### 5.1.20. *tert*-Butyl 4-{[2-(4-fluorophenyl)-2-methylpropyl] carbamoyl}piperidine-1-carboxylate (19a)

To an ice-cooled mixture of sodium hydride (60% dispersion in mineral oil; 1.25 g, 31.3 mmol) and iodomethane (2.2 ml,

35.3 mmol) in DMF (15 ml) was added dropwise a solution of 4-fluorophenylacetonitrile (**3**, 2.0 g, 14.8 mmol) and DMF (5.0 ml) and the mixture was stirred at room temperature for two days. The mixture was poured onto 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 (AcOEt/hexane = 1/40) to give 2-(4-fluorophenyl)-2-methylpropanenitrile (2.11 g, 87%) as a colorless oil. To a suspension of Raney–Ni (ca 0.50 g) and 28 w/w% $NH_4OH$ (2.0 ml) in EtOH (15 ml) was added the nitrile obtained above (2.11 g, 12.9 mmol) and the mixture was stirred under hydrogen atmosphere at room temperature for 20 h. The catalyst was removed by filtration and the filtrate was concentrated in vacuo to give 2-(4-fluorophenyl)-2-methylpropan-1-amine (2.07 g, 96%) as a light yellow oil. To an ice-cooled solution of the amine obtained above (0.60 g, 3.59 mmol), 1-(Boc)piperidine-4-carboxylic acid (0.90 g, 3.93 mmol), and HOBt (0.50 g, 3.70 mmol) in DMF (10 ml) was added WSCD (0.75 g, 3.91 mmol) and the mixture was stirred at room temperature for three days. 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 = 1/1) to give the title compound **19a** (1.27 g, 93%) as a light yellow foam.

$^1$H NMR ($CDCl_3$) $\delta$: 1.31 (6H, s), 1.44 (9H, s), 1.45–1.70 (4H, m), 2.04–2.13 (1H, m), 2.62–2.75 (2H, m), 3.45 (2H, d, $J$ = 6.4 Hz), 4.08 (2H, br d, $J$ = 13.5 Hz), 5.09 (1H, br s), 7.03 (2H, dd, $J$ = 8.4, 8.8 Hz), 7.30 (2H, dd, $J$ = 5.2, 8.8 Hz). MS (FAB) $m/z$: 379 ($M^+$+1).

#### 5.1.21. *tert*-Butyl 4-{[2-ethyl-2-(4-fluorophenyl)butyl] carbamoyl}piperidine-1-carboxylate (19b)

The title compound was prepared in the same manner as described for **20a** using iodoethane instead of iodomethane, in 92% yield.

$^1$H NMR ($CDCl_3$) $\delta$: 0.75 (6H, t, $J$ = 7.6 Hz), 1.44 (9H, s), 1.45–1.71 (8H, m), 2.00–2.12 (1H, m), 2.62–2.75 (2H, m), 3.51 (2H, d, $J$ = 6.0 Hz), 4.08 (2H, br s), 4.95 (1H, br s), 7.05 (2H, dd, $J$ = 8.4, 8.8 Hz), 7.27 (2H, dd, $J$ = 5.2, 8.8 Hz). MS (FAB) $m/z$: 407 ($M^+$+1).

#### 5.1.22. *tert*-Butyl 4-{[2-(4-fluorophenyl)-2-propylpentyl] carbamoyl}piperidine-1-carboxylate (19c)

The title compound was prepared in the same manner as described for **20a** using iodopropane instead of iodomethane, in 35% yield.

$^1$H NMR ($CDCl_3$) $\delta$: 0.87 (6H, t, $J$ = 7.6 Hz), 1.02–1.27 (4H, m), 1.44 (9H, s), 1.45–1.71 (8H, m), 2.00–2.12 (1H, m), 2.62–2.75 (2H, m), 3.51 (2H, d, $J$ = 5.6 Hz), 4.07 (2H, br d, $J$ = 13.6 Hz), 4.95 (1H, br s), 7.04 (2H, dd, $J$ = 8.4, 8.8 Hz), 7.27 (2H, dd, $J$ = 5.2, 8.8 Hz). MS (FAB) $m/z$: 435 ($M^+$+1).

#### 5.1.23. 1-Benzyl-*N*-[2-(4-fluorophenyl)-2-methylpropyl] piperidine-4-carboxamide hydrochloride (20a)

The title compound was prepared in the same manner as described for **5a** using **19a** instead of **4a**, in 53% yield.

$^1$H NMR (DMSO-$d_6$) $\delta$: 1.21 (6H, s), 1.69–2.00 (4H, m), 2.28–2.41 (1H, m), 2.75–3.00 (2H, m), 3.05–3.35 (4H, m), 4.20–4.29 (2H, m), 7.09 (2H, dd, $J$ = 8.4, 8.6 Hz), 7.36 (2H, dd, $J$ = 5.3, 8.6 Hz), 7.43–7.48 (3H, m), 7.55–7.65 (2H, m), 7.72 and 7.80 (1H, t, $J$ = 5.9 Hz), 10.35 and 10.75 (1H, br s). MS (FAB) $m/z$: 369 ($M^+$+1). Anal. Calcd for $C_{23}H_{29}N_2OF{\cdot}HCl$: C, 68.22; H, 7.47; N, 6.92; Cl, 8.75; F, 4.69. Found: C, 68.08; H, 7.55; N, 6.91; Cl, 8.78; F, 4.63.

#### 5.1.24. 1-Benzyl-*N*-[2-ethyl-2-(4-fluorophenyl)butyl]piperidine-4-carboxamide hydrochloride (20b)

The title compound was prepared in the same manner as described for **5a** using **19b** instead of **4a**, in 58% yield.

$^1$H NMR (DMSO-$d_6$) $\delta$: 0.60 (6H, t, $J$ = 7.3 Hz), 1.61 (4H, q, $J$ = 7.3 Hz), 1.69–2.00 (4H, m), 2.34–2.45 (1H, m), 2.75–3.00 (2H, m), 3.26–3.41 (4H, m), 4.20–4.29 (2H, m), 7.10 (2H, dd, $J$ = 8.4, 8.8 Hz), 7.29 (2H, dd, $J$ = 5.8, 8.8 Hz), 7.42–7.50 (4H, m), 7.55–7.64 (2H, m), 10.41 and 10.82 (1H, br s). MS (FAB) $m/z$: 397 ($M^+$+1). Anal. Calcd for $C_{25}H_{33}N_2OF{\cdot}HCl$: C, 69.35; H, 7.91; N, 6.47; Cl, 8.19; F, 4.39. Found: C, 69.19; H, 7.92; N, 6.32; Cl, 8.10; F, 4.42.

#### 5.1.25. 1-Benzyl-*N*-[2-(4-fluorophenyl)-2-propylpentyl] piperidine-4-carboxamide hydrochloride (20c)

The title compound was prepared in the same manner as described for **5a** using **19c** instead of **4a**, in 73% yield.

$^1$H NMR (DMSO-$d_6$) $\delta$: 0.78 (6H, t, $J$ = 7.0 Hz), 0.84–1.10 (4H, m), 1.52 (4H, t, $J$ = 8.1 Hz), 1.69–2.00 (4H, m), 2.34–2.45 (1H, m), 2.75–3.00 (2H, m), 3.28–3.41 (4H, m), 4.20–4.30 (2H, m), 7.09 (2H, dd, $J$ = 8.4, 8.6 Hz), 7.29 (2H, dd, $J$ = 5.4, 8.6 Hz), 7.42–7.52 (4H, m), 7.54–7.62 (2H, m), 10.22 and 10.68 (1H, br s). MS (FAB) $m/z$: 425 ($M^+$+1). Anal. Calcd for $C_{27}H_{37}N_2OF{\cdot}HCl{\cdot}0.5H_2O$: C, 68.99; H, 8.36; N, 5.96; Cl, 7.54; F, 4.04. Found: C, 69.25; H, 8.46; N, 5.99; Cl, 7.68; F, 4.02.

#### 5.1.26. *N*-[2-Ethyl-2-(4-fluorophenyl)butyl]-1-(2-phenylethyl) piperidine-4-carboxamide hydrochloride (20d)

To an ice-cooled solution of **19b** (1.81 g, 4.45 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 18 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 converted to its oxalate by treating it with oxalic acid (0.40 g, 4.44 mmol). The crude salt was suspended with $CH_3CN$ and filtered to give *N*-[2-ethyl-2-(4-fluorophenyl)butyl]piperidine-4-carboxamide oxalate (1.71 g, 97%) as a colorless solid. To an ice-cooled mixture of the piperidine derivative obtained above (0.40 g, 1.01 mmol) and phenylacetaldehyde (0.20 ml, 1.79 mmol) in $CH_2Cl_2$ (5.0 ml) was added sodium triacetoxyborohydride (0.44 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 $CHCl_3$. 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*-[2-ethyl-2-(4-fluorophenyl)butyl]-1-(2-phenylethyl)piperidine-4-carboxamide (0.44 g) as a colorless solid. The compound was converted to its hydrochloride salt by treating it with 4 M HCl–AcOEt (0.30 ml, 1.20 mmol). The crude salt was suspended with AcOEt and filtered to give the title compound **20d** (0.32 g, 72%) as a colorless powder.

$^1$H NMR (DMSO-$d_6$) $\delta$: 0.61 (6H, t, $J$ = 7.3 Hz), 1.63 (4H, q, $J$ = 7.3 Hz), 1.72–1.90 (4H, m), 2.36–2.47 (1H, m), 2.75–2.92 (2H, m), 2.97–3.07 (2H, m), 3.20–3.30 (2H, m), 3.41 (2H, d, $J$ = 5.8 Hz), 3.53–3.60 (2H, m), 7.12 (2H, dd, $J$ = 8.4, 8.8 Hz), 7.24–7.37 (7H, m), 7.47–7.57 (1H, m), 10.15 and 10.56 (1H, br s). MS (FAB) $m/z$: 411 ($M^+$+1). Anal. Calcd for $C_{26}H_{35}N_2OF{\cdot}HCl$: C, 69.86; H, 8.12; N, 6.27; Cl, 7.93; F, 4.25. Found: C, 69.71; H, 8.07; N, 6.04; Cl, 7.96; F, 4.23.

#### 5.1.27. *N*-[2-Ethyl-2-(4-fluorophenyl)butyl]-1-(3-phenylpropyl) piperidine-4-carboxamide oxalate (20e) (Method A)

To an ice-cooled mixture of *N*-[2-ethyl-2-(4-fluorophenyl) butyl]piperidine-4-carboxamide oxalate (0.50 g, 1.26 mmol) and

hydrocinnamaldehyde (0.21 g, 1.57 mmol) in $CH_2Cl_2$ (5.0 ml) was added sodium triacetoxyborohydride (0.54 g, 2.55 mmol) and the mixture was stirred at room temperature for 15 h. The reaction mixture was concentrated in vacuo and the resulting residue was 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/$CHCl_3$ = 5/95) to give *N*-[2-ethyl-2-(4-fluorophenyl)butyl]-1-(3-phenylpropyl) piperidine-4-carboxamide (0.48 g) as a colorless oil. The compound was converted to its oxalate by treating it with oxalic acid (0.10 g, 1.11 mmol). The crude salt was suspended with $CH_3CN$ and filtered to give the title compound **20e** (0.45 g, 77%) as a colorless powder.

$^1$H NMR (DMSO-$d_6$) $\delta$: 0.60 (6H, t, $J$ = 8.0 Hz), 1.61 (4H, q, $J$ = 8.0 Hz), 1.65–1.75 (4H, m), 1.85–1.98 (2H, m), 2.35–2.45 (1H, m), 2.61 (2H, t, $J$ = 7.6 Hz), 2.75 (2H, br s), 2.88–3.00 (2H, m), 3.28–3.44 (4H, m), 7.11 (2H, dd, $J$ = 8.4, 8.8 Hz), 7.18–7.33 (7H, m), 7.48 (1H, t, $J$ = 6.0 Hz). MS (FAB) *m/z*: 425 ($M^+$+1). Anal. Calcd for $C_{27}H_{37}N_2OF{\cdot}C_2H_2O_4{\cdot}0.3H_2O$: C, 66.98; H, 7.68; N, 5.39; F, 3.65. Found: C, 66.99; H, 7.65; N, 5.29; F, 3.62.

### 5.1.28. *N*-[2-Ethyl-2-(4-fluorophenyl)butyl]-1-(4-phenylbutyl) piperidine-4-carboxamide hydrochloride (20f) (Method B)

To a mixture of *N*-[2-ethyl-2-(4-fluorophenyl)butyl]piperidine-4-carboxamide oxalate (0.40 g, 958 μmol) in $CHCl_3$ (20 ml) was added saturated aqueous sodium bicarbonate solution (15 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 *N*-[2-ethyl-2-(4-fluorophenyl)butyl]piperidine-4-carboxamide (0.30 g) as a colorless oil, which was used for the next step without further purification. To a mixture of the piperidine derivative obtained above (0.30 g, 979 μmol) and $K_2CO_3$ (0.20 g, 1.44 mmol) in $CH_3CN$ (10 ml) was added (4-bromobutyl)benzene (0.27 g, 1.27 mmol) and the mixture was stirred at 60 °C for 15 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*-[2-ethyl-2-(4-fluorophenyl)butyl]-1-(4-phenylbutyl)piperidine-4-carboxamide (0.29 g) as a colorless solid. The compound was converted to its hydrochloride salt by treating it with 4 M HCl–AcOEt (0.25 ml, 1.00 mmol). The crude salt was suspended with AcOEt and filtered to give the title compound **20f** (0.21 g, 49%) as a colorless powder.

$^1$H NMR (DMSO-$d_6$) $\delta$: 0.60 (6H, t, $J$ = 7.2 Hz), 1.52–1.84 (12H, m), 2.34–2.46 (1H, m), 2.61 (2H, t, $J$ = 7.2 Hz), 2.70–2.85 (2H, m), 2.90–3.06 (2H, m), 3.35–3.50 (4H, m), 7.11 (2H, dd, $J$ = 8.4, 8.8 Hz), 7.15–7.24 (3H, m), 7.24–7.34 (4H, m), 7.49 and 7.54 (1H, t, $J$ = 6.4 Hz), 9.44 and 9.86 (1H, br s). MS (FAB) *m/z*: 439 ($M^+$+1). Anal. Calcd for $C_{28}H_{39}N_2OF{\cdot}HCl$: C, 70.79; H, 8.49; N, 5.90; Cl, 7.46; F, 4.00. Found: C, 70.52; H, 8.72; N, 5.88; Cl, 7.49; F, 3.82.

### 5.1.29. *N*-[2-Ethyl-2-(4-fluorophenyl)butyl]-1-(2-phenoxyethyl) piperidine-4-carboxamide oxalate (20g)

The title compound was prepared in the same manner as described for **20f** using (2-bromoethoxy)benzene instead of (4-bromobutyl)benzene, in 33% yield.

$^1$H NMR (DMSO-$d_6$) $\delta$: 0.60 (6H, t, $J$ = 7.2 Hz), 1.61 (4H, q, $J$ = 7.2 Hz), 1.69–1.77 (4H, m), 2.34–2.46 (1H, m), 2.81 (2H, br s), 3.28–3.44 (6H, m), 4.27 (2H, t, $J$ = 5.2 Hz), 6.95–7.00 (3H, m), 7.11 (2H, dd, $J$ = 8.4, 8.8 Hz), 7.27–7.34 (4H, m), 7.46 (1H, t, $J$ = 5.6 Hz). MS (ESI) *m/z*: 427 ($M^+$+1). Anal. Calcd for $C_{26}H_{35}N_2O_2F{\cdot}C_2H_2O_4$: C, 65.10; H, 7.22; N, 5.42; F, 3.68. Found: C, 64.92; H, 7.35; N, 6.14; F, 3.39.

### 5.1.30. *N*-[2-Ethyl-2-(4-fluorophenyl)butyl]-1-(2-fluorobenzyl) piperidine-4-carboxamide hydrochloride (20h)

The title compound was prepared in the same manner as described for **20e** using 2-fluorobenzaldehyde instead of hydrocinnamaldehyde, in 67% yield.

$^1$H NMR (DMSO-$d_6$) $\delta$: 0.60 (6H, t, $J$ = 7.2 Hz), 1.61 (4H, q, $J$ = 7.2 Hz), 1.70–1.90 (4H, m), 2.35–2.46 (1H, m), 2.82–3.00 (2H, m), 3.33–3.41 (4H, m), 4.25–4.34 (2H, m), 7.10 (2H, dd, $J$ = 8.4, 8.8 Hz), 7.25–7.37 (4H, m), 7.44–7.58 (2H, m), 7.78 (1H, t, $J$ = 7.2 Hz), 10.60 and 11.08 (1H, br s). MS (FAB) *m/z*: 415 ($M^+$+1). Anal. Calcd for $C_{25}H_{32}N_2OF_2{\cdot}HCl{\cdot}0.3H_2O$: C, 65.79; H, 7.42; N, 6.14; Cl, 7.77; F, 8.33. Found: C, 65.99; H, 7.47; N, 6.13; Cl, 7.66; F, 8.29.

### 5.1.31. *N*-[2-Ethyl-2-(4-fluorophenyl)butyl]-1-(3-fluorobenzyl) piperidine-4-carboxamide hydrochloride (20i)

The title compound was prepared in the same manner as described for **20e** using 3-fluorobenzaldehyde instead of hydrocinnamaldehyde, in 67% yield.

$^1$H NMR (DMSO-$d_6$) $\delta$: 0.60 (6H, t, $J$ = 7.2 Hz), 1.61 (4H, q, $J$ = 7.2 Hz), 1.70–1.88 (4H, m), 2.35–2.45 (1H, m), 2.75–2.88 (2H, m), 3.28–3.41 (4H, m), 4.25–4.34 (2H, m), 7.10 (2H, dd, $J$ = 8.4, 8.8 Hz), 7.25–7.34 (3H, m), 7.37–7.60 (4H, m), 10.37 and 10.79 (1H, br s). MS (FAB) *m/z*: 415 ($M^+$+1). Anal. Calcd for $C_{25}H_{32}N_2OF_2{\cdot}HCl{\cdot}0.4H_2O$: C, 65.53; H, 7.44; N, 6.11; Cl, 7.74; F, 8.29. Found: C, 65.48; H, 7.50; N, 6.13; Cl, 7.98; F, 8.33.

### 5.1.32. *N*-[2-Ethyl-2-(4-fluorophenyl)butyl]-1-(4-fluorobenzyl) piperidine-4-carboxamide hydrochloride (20j)

The title compound was prepared in the same manner as described for **20e** using 4-fluorobenzaldehyde instead of hydrocinnamaldehyde, in 56% yield.

$^1$H NMR (DMSO-$d_6$) $\delta$: 0.60 (6H, t, $J$ = 7.2 Hz), 1.61 (4H, q, $J$ = 7.2 Hz), 1.69–1.86 (4H, m), 2.34–2.44 (1H, m), 2.73–2.87 (2H, m), 3.26–3.42 (4H, m), 4.22–4.30 (2H, m), 7.10 (2H, dd, $J$ = 8.4, 8.8 Hz), 7.25–7.34 (4H, m), 7.46 (1H, t, $J$ = 5.6 Hz), 7.64 (2H, dd, $J$ = 5.2, 8.0 Hz), 10.36 and 10.77 (1H, br s). MS (FAB) *m/z*: 415 ($M^+$+1). Anal. Calcd for $C_{25}H_{32}N_2OF_2{\cdot}HCl$: C, 66.58; H, 7.38; N, 6.21; Cl, 7.86; F, 8.43. Found: C, 66.44; H, 7.48; N, 6.19; Cl, 8.11; F, 8.37.

### 5.1.33. *N*-[2-Ehyl-2-(4-fluorophenyl)butyl]-1-(2-methoxybenzyl)piperidine-4-carboxamide oxalate (20k)

The title compound was prepared in the same manner as described for **20e** using 2-methoxybenzaldehyde instead of hydrocinnamaldehyde, in 52% yield.

$^1$H NMR (DMSO-$d_6$) $\delta$: 0.60 (6H, t, $J$ = 7.2 Hz), 1.61 (4H, q, $J$ = 7.2 Hz), 1.67–1.77 (4H, m), 2.33–2.44 (1H, m), 2.76 (2H, br s), 3.17–3.27 (2H, m), 3.38 (2H, d, $J$ = 6.4 Hz), 3.82 (3H, s), 4.10 (2H, s), 7.00 (1H, t, $J$ = 6.4 Hz), 7.06–7.14 (3H, m), 7.29 (2H, dd, $J$ = 5.6, 8.8 Hz), 7.38–7.45 (3H, m). MS (FAB) *m/z*: 427 ($M^+$+1). Anal. Calcd for $C_{26}H_{35}N_2O_2F{\cdot}C_2H_2O_4{\cdot}0.2H_2O$: C, 64.65; H, 7.25; N, 5.39; F, 3.65. Found: C, 64.59; H, 7.26; N, 5.39; F, 3.65.

### 5.1.34. *N*-[2-Ehyl-2-(4-fluorophenyl)butyl]-1-(3-methoxybenzyl)piperidine-4-carboxamide oxalate (20l)

The title compound was prepared in the same manner as described for **20e** using 3-methoxybenzaldehyde instead of hydrocinnamaldehyde, in 62% yield.

$^1$H NMR (DMSO-$d_6$) $\delta$: 0.60 (6H, t, $J$ = 7.2 Hz), 1.61 (4H, q, $J$ = 7.2 Hz), 1.67–1.76 (4H, m), 2.32–2.42 (1H, m), 2.67 (2H, br s), 3.12–3.23 (2H, m), 3.38 (2H, d, $J$ = 6.4 Hz), 3.77 (3H, s), 4.06 (2H, s), 6.95–7.13 (5H, m), 7.26–7.36 (3H, m), 7.43 (1H, t, $J$ = 6.4 Hz). MS (FAB) *m/z*: 427 ($M^+$+1). Anal. Calcd for $C_{26}H_{35}N_2O_2F{\cdot}C_2H_2O_4{\cdot}0.3H_2O$: C, 64.42; H, 7.26; N, 5.37; F, 3.64. Found: C, 64.39; H, 7.19; N, 5.40; F, 3.61.

#### 5.1.35. *N*-[2-Ehyl-2-(4-fluorophenyl)butyl]-1-(4-methoxybenzyl)piperidine-4-carboxamide oxalate (20m)

The title compound was prepared in the same manner as described for **20e** using 4-methoxybenzaldehyde instead of hydrocinnamaldehyde, in 34% yield.

$^1$H NMR (DMSO-$d_6$) $\delta$: 0.60 (6H, t, $J$ = 7.6 Hz), 1.61 (4H, q, $J$ = 7.6 Hz), 1.64–1.75 (4H, m), 2.28–2.40 (1H, m), 2.64 (2H, br s), 3.09–3.23 (2H, m), 3.38 (2H, d, $J$ = 6.0 Hz), 3.77 (3H, s), 4.03 (2H, s), 6.97 (2H, d, $J$ = 8.8 Hz), 7.10 (2H, dd, $J$ = 8.4, 8.8 Hz), 7.29 (2H, dd, $J$ = 5.2, 8.8 Hz), 7.36 (2H, d, $J$ = 8.8 Hz), 7.42 (1H, t, $J$ = 6.0 Hz). MS (FAB) *m/z*: 427 ($M^+$+1). Anal. Calcd for $C_{26}H_{35}N_2O_2F\cdot C_2H_2O_4\cdot 0.5H_2O$: C, 63.98; H, 7.29; N, 5.33; F, 3.61. Found: C, 63.99; H, 7.10; N, 5.35; F, 3.60.

#### 5.1.36. *N*-[2-Ethyl-2-(4-fluorophenyl)butyl]-1-[2-(2-fluorophenyl)ethyl]piperidine-4-carboxamide oxalate (20n)

The title compound was prepared in the same manner as described for **20e** using (2-fluorophenyl)acetaldehyde instead of hydrocinnamaldehyde, in 32% yield.

$^1$H NMR (DMSO-$d_6$) $\delta$: 0.61 (6H, t, $J$ = 7.6 Hz), 1.62 (4H, q, $J$ = 7.6 Hz), 1.67–1.80 (4H, m), 2.36–2.45 (1H, m), 2.77 (2H, br s), 2.94–3.02 (2H, m), 3.06–3.15 (2H, m), 3.35–3.46 (4H, m), 7.11 (2H, dd, $J$ = 8.4, 8.8 Hz), 7.15–7.23 (2H, m), 7.27–7.38 (4H, m), 7.48 (1H, t, $J$ = 6.0 Hz). MS (FAB) *m/z*: 429 ($M^+$+1). Anal. Calcd for $C_{26}H_{34}N_2OF_2\cdot C_2H_2O_4\cdot 0.3H_2O\cdot 0.2CH_3CN$: C, 64.09; H, 7.05; N, 5.79; F, 7.05. Found: C, 64.04; H, 7.12; N, 5.81; F, 7.18.

#### 5.1.37. *N*-[2-Ethyl-2-(4-fluorophenyl)butyl]-1-[2-(3-fluorophenyl)ethyl]piperidine-4-carboxamide oxalate (20o)

The title compound was prepared in the same manner as described for **20f** using 2-(3-fluorophenyl)ethyl *p*-toluenesulfonate instead of (4-bromobutyl)benzene, in 50% yield.

$^1$H NMR (DMSO-$d_6$) $\delta$: 0.61 (6H, t, $J$ = 7.6 Hz), 1.62 (4H, q, $J$ = 7.6 Hz), 1.67–1.80 (4H, m), 2.36–2.46 (1H, m), 2.76 (2H, br s), 2.92–3.01 (2H, m), 3.10–3.21 (2H, m), 3.32–3.46 (4H, m), 7.04–7.16 (5H, m), 7.28–7.40 (3H, m), 7.47 (1H, t, $J$ = 6.0 Hz). MS (FAB) *m/z*: 429 ($M^+$+1). Anal. Calcd for $C_{26}H_{34}N_2OF_2\cdot C_2H_2O_4\cdot 0.4H_2O$: C, 63.96; H, 7.05; N, 5.33; F, 7.23. Found: C, 64.06; H, 7.03; N, 5.34; F, 7.21.

#### 5.1.38. *N*-[2-Ethyl-2-(4-fluorophenyl)butyl]-1-[2-(4-fluorophenyl)ethyl]piperidine-4-carboxamide hydrochloride (20p)

The title compound was prepared in the same manner as described for **20f** using 2-(4-fluorophenyl)ethyl *p*-toluenesulfonate instead of (4-bromobutyl)benzene, in 65% yield.

$^1$H NMR (DMSO-$d_6$) $\delta$: 0.61 (6H, t, $J$ = 7.6 Hz), 1.62 (4H, q, $J$ = 7.6 Hz), 1.72–1.90 (4H, m), 2.38–2.50 (1H, m), 2.76–2.90 (2H, m), 3.00–3.08 (2H, m), 3.18–3.27 (2H, m), 3.40 (2H, d, $J$ = 6.0 Hz), 3.50–3.58 (2H, m), 7.08–7.21 (4H, m), 7.27–7.35 (4H, m), 7.52 (1H, t, $J$ = 6.0 Hz), 10.40 and 10.79 (1H, br s). MS (FAB) *m/z*: 429 ($M^+$+1). Anal. Calcd for $C_{26}H_{34}N_2OF_2\cdot HCl\cdot 0.7H_2O$: C, 65.38; H, 7.68; N, 5.87; Cl, 7.42; F, 7.96. Found: C, 65.39; H, 7.80; N, 5.84; Cl, 7.32; F, 8.29.

#### 5.1.39. *N*-[2-Ethyl-2-(4-fluorophenyl)butyl]-1-[2-(2-methoxyphenyl)ethyl]piperidine-4-carboxamide oxalate (20q)

The title compound was prepared in the same manner as described for **20e** using (2-methoxyphenyl)acetaldehyde instead of hydrocinnamaldehyde, in 62% yield.

$^1$H NMR (DMSO-$d_6$) $\delta$: 0.61 (6H, t, $J$ = 7.6 Hz), 1.62 (4H, q, $J$ = 7.6 Hz), 1.67–1.80 (4H, m), 2.36–2.46 (1H, m), 2.74–2.96 (4H, m), 3.04–3.15 (2H, m), 3.35–3.50 (4H, m), 3.80 (3H, s), 6.91 (1H, dd, $J$ = 6.8, 6.8 Hz), 6.99 (1H, d, $J$ = 8.0 Hz), 7.12 (2H, dd, $J$ = 8.4, 8.8 Hz), 7.15–7.34 (4H, m), 7.49 (1H, t, $J$ = 6.0 Hz). MS (ESI) *m/z*: 441 ($M^+$+1). Anal. Calcd for $C_{27}H_{37}N_2O_2F\cdot C_2H_2O_4\cdot 0.5H_2O$: C, 64.55; H, 7.47; N, 5.19; F, 3.52. Found: C, 64.64; H, 7.44; N, 4.98; F, 3.53.

#### 5.1.40. *N*-[2-Ethyl-2-(4-fluorophenyl)butyl]-1-[2-(3-methoxyphenyl)ethyl]piperidine-4-carboxamide oxalate (20r)

The title compound was prepared in the same manner as described for **20e** using (3-methoxyphenyl)acetaldehyde instead of hydrocinnamaldehyde, in 11% yield.

$^1$H NMR (DMSO-$d_6$) $\delta$: 0.61 (6H, t, $J$ = 7.6 Hz), 1.62 (4H, q, $J$ = 7.6 Hz), 1.67–1.80 (4H, m), 2.36–2.45 (1H, m), 2.76 (2H, br s), 2.85–2.95 (2H, m), 3.06–3.20 (2H, m), 3.32–3.48 (4H, m), 3.74 (3H, s), 6.79–6.86 (3H, m), 7.11 (2H, dd, $J$ = 8.4, 8.8 Hz), 7.20–7.34 (3H, m), 7.47 (1H, t, $J$ = 6.0 Hz). MS (ESI) *m/z*: 441 ($M^+$+1). Anal. Calcd for $C_{27}H_{37}N_2O_2F\cdot C_2H_2O_4$: C, 65.64; H, 7.41; N, 5.28; F, 3.58. Found: C, 65.45; H, 7.37; N, 5.09; F, 3.57.

#### 5.1.41. *N*-[2-Ethyl-2-(4-fluorophenyl)butyl]-1-[2-(4-methoxyphenyl)ethyl]piperidine-4-carboxamide oxalate (20s)

The title compound was prepared in the same manner as described for **20e** using (4-methoxyphenyl)acetaldehyde instead of hydrocinnamaldehyde, in 50% yield.

$^1$H NMR (DMSO-$d_6$) $\delta$: 0.61 (6H, t, $J$ = 7.6 Hz), 1.62 (4H, q, $J$ = 7.6 Hz), 1.67–1.80 (4H, m), 2.37–2.46 (1H, m), 2.70–2.90 (4H, m), 3.06–3.15 (2H, m), 3.32–3.48 (4H, m), 3.73 (3H, s), 6.88 (2H, d, $J$ = 8.8 Hz), 7.12 (2H, dd, $J$ = 8.4, 8.8 Hz), 7.17 (2H, d, $J$ = 8.8 Hz), 7.30 (2H, dd, $J$ = 5.2, 8.8 Hz), 7.48 (1H, t, $J$ = 6.0 Hz). MS (ESI) *m/z*: 441 ($M^+$+1). Anal. Calcd for $C_{27}H_{37}N_2O_2F\cdot C_2H_2O_4\cdot 0.3H_2O\cdot 0.5CH_3CN$: C, 64.74; H, 7.44; N, 6.29; F, 3.41. Found: C, 64.74; H, 7.34; N, 6.36; F, 3.37.

### 5.2. Pharmacology

#### 5.2.1. T-type $Ca^{2+}$ channel blocking activity study

HEK293 cells stably expressing human Cav3.1 (alpha1G) were maintained in D-MEM supplemented with 10% (v/v) fetal bovine serum, penicillin (100 U/ml), streptomycin (100 μg/ml), geneticin (600 μg/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 a density of 25,000 cells/well. Hanks balanced salt solution, containing 1.3 mM $CaCl_2$, 20 mM HEPES and 2.5 mM probenecid was used as the assay buffer. The growth medium was removed and replaced with dye loading buffer (100 μl/well) containing 4 μM fluo-3 AM, 0.04% Pluronic acid F-127, 1% fetal bovine serum in the assay buffer. After the 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 assay buffer in each well of 100 μl. The plates were left to stand at room temperature for 10 min before assay, after which the plates were placed into a FLIPR™ apparatus (Molecular Devices, Berkshire, UK) to monitor cell fluorescence. Test compounds (50 μl 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+ μM. The $IC_{50}$ value was calculated using a non-linear regression method, taking the maximum reaction value as 100%.

#### 5.2.2. 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 babbled 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 DMSO and diluted with saline to the desired concentration were added to the bath solution cumulatively at 30-min intervals to construct a concentration–response curve. The $EC_{30}$ value for the concentration of the compounds producing a 30% reduction from initial spontaneous beat rate was determined via linear regression.

### 5.2.3. Pharmacology in vivo study (po)

Male SHR rats (300–350 g) were anesthetized with pentobarbital (60 mg/kg ip), 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 cardiotachometer (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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