# Synthesis and Pharmacological Evaluation of 2-(1-Alkylpiperidin-4-yl)-*N*-[(1*R*)-1-(4-fluorophenyl)-2-methylpropyl]acetamide Derivatives as Novel Antihypertensive Agents

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Received October 25, 2011; accepted November 28, 2011; published online November 29, 2011

**We synthesized and evaluated the inhibitory activity of a series of 2-(1-alkylpiperidin-4-yl)-*N*-[(1*R*)-1-(4-fluorophenyl)-2-methylpropyl]acetamide derivatives against T-type $Ca^{2+}$ channels. Structure–activity relationship studies revealed that the position of the amide structure was important for the potent inhibitory activity toward T-type $Ca^{2+}$ channels. In addition, the introduction of an appropriate substituent on the pendant benzene ring played a crucial role for the selectivity towards T-type $Ca^{2+}$ channels over L-type $Ca^{2+}$ channels and the potent bradycardic activity of these derivatives. Oral administration of *N*-[(1*R*)-1-(4-fluorophenyl)-2-methylpropyl]-2-(1-{2-[2-(2-methoxyethoxy)phenyl]ethyl}piperidin-4-yl)acetamide (4f), which had superior selectivity for T-type $Ca^{2+}$ channels over L-type $Ca^{2+}$ channels, lowered blood pressure in spontaneously hypertensive rats without inducing reflex tachycardia, which is often caused by traditional L-type $Ca^{2+}$ channel blockers.**

**Key words** antihypertensive agent; T-type $Ca^{2+}$ channel; mibefradil; 2-(piperidin-4-yl)acetamide

Numerous cardiovascular disorders, including hypertension, angina, heart failure, and arrhythmia, are associated with 'calcium overload' resulting from abnormally elevated calcium influx through the plasma membrane of cardiac and vascular smooth muscle cells. Three major pathways by which extracellular calcium can enter cells have been identified: 1) receptor-activated calcium channels, 2) ligand-gated calcium channels, and 3) voltage-operated calcium (VOC) channels.[1)]

VOC channels are found in the nervous, endocrine, cardiovascular, and skeletal systems, and are classified into six main categories: L (long-lasting), T (transient), N (neuronal), P (Purkinje cells), Q (after P), and R (remaining or resistant).[2,3)] L- and T-type channels, in particular, are proposed to be associated with several cardiovascular diseases. L-type $Ca^{2+}$ channels are responsible for the inward movement of $Ca^{2+}$, which initiates contraction in cardiac and smooth muscle cells. Therefore, L-type $Ca^{2+}$ channel blockers are currently recommended as first-line treatment for hypertension and angina.[4)] In contrast, T-type $Ca^{2+}$ channels are thought to contribute to the regulation of cardiovascular activities including heart rate (HR), and arterial and venous smooth muscle intervention and tone.[5)]

Nearly all therapeutic $Ca^{2+}$ channel blockers currently on the market have selective effects on L-type over T-type $Ca^{2+}$ channels. However, mibefradil (**1**) was reported to show 10- to 30-fold higher selectivity for T-type $Ca^{2+}$ channels.[6,7)] Due to the selective inhibiton of T-type $Ca^{2+}$ channels, mibefradil demonstrated superior outcome over traditional L-type $Ca^{2+}$ channel blockers for treating hypertension and angina, and notably, the adverse effects often associated with L-type $Ca^{2+}$ channel blockers, such as reflex tachycardia, negative inotropy, vasoconstrictive hormone release, and peripheral edema, were not reported.[8)] However, it is unclear whether the unique effects of mibefradil are caused by the blockage of T-type $Ca^{2+}$ channels as mibefradil also blocks L-type $Ca^{2+}$ channels a limited extent. Therefore, identifying T-type $Ca^{2+}$ channel blockers with greater selectivity will be useful for elucidating the role of these channels and may lead to the development of a novel class of therapeutically beneficial compounds.[9—41)]

We recently reported the synthesis and pharmacological evaluation of several piperidine derivatives of T-type $Ca^{2+}$ channel blockers (Table 1).[42—44)] Compounds **2** and **3** exhibited potent inhibitory activities against T-type $Ca^{2+}$ channels, and on oral administration to spontaneously hypertensive rats, elicited antihypertensive effects without inducing reflex tachycardia. To confirm whether the antihypertensive effects were a result of the blockage of T-type $Ca^{2+}$ channels, we preliminarily evaluated the inhibitory activity of these compounds against L-type $Ca^{2+}$ channels (Table 1). Although mibefradil (**1**) showed moderate inhibitory activity against L-type $Ca^{2+}$ channels ($IC_{50}$=1.1 $\mu$M) and marginal selectivity for T- over L-type $Ca^{2+}$ channels (L/T=5.5), compounds **2** and **3** exhibited superior selectivity for T-type $Ca^{2+}$ channels (L/T=49, 29, respectively), but still had moderate L-type $Ca^{2+}$ channel inhibitory activities ($IC_{50}$=4.4, 2.2 $\mu$M, respectively). To obtain a T-type $Ca^{2+}$ channel blocker with greater selectivity, we modified piperidine derivatives by various approaches. After extensive experimentation, we identified that the 2-(piperidin-4-yl) acetamide derivative **4a** exhibited potent inhibitory activity against T-type $Ca^{2+}$ channels ($IC_{50}$=0.062 $\mu$M) and excellent selectivity over L-type $Ca^{2+}$ channels ($IC_{50}$=10 $\mu$M, L/T=161).

Encouraged by these data, we conducted further modification of **4a**. In this paper, we describe the synthesis, structure–activity relationships, and pharmacological properties of 2-(1-alkylpiperidin-4-yl)-*N*-[(1*R*)-1-(4-fluorophenyl)-2-methylpropyl]acetamide derivatives as novel T-type $Ca^{2+}$ channel blocking agents with high selectivity vs L-type $Ca^{2+}$ channels.

**Synthesis** The preparation of the 2-(1-alkylpiperidin-4-yl)-*N*-[(1*R*)-1-(4-fluorophenyl)-2-methylpropyl]acetamide derivatives are outlined in Chart 1. Condensation of opti-

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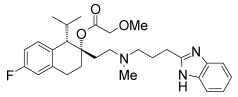
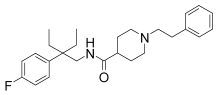
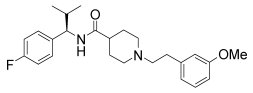
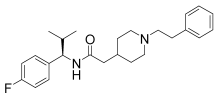
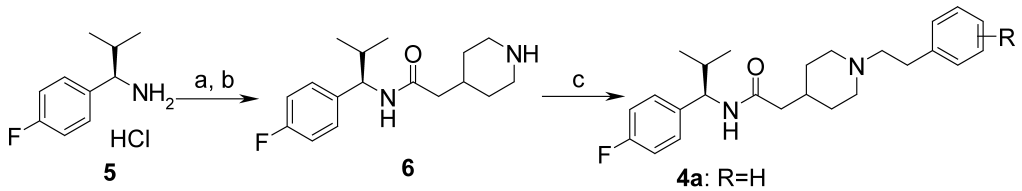
Table 1. $Ca^{2+}$ Channel Blocking Activity of Selected Compounds (**1**—**3**, **4a**)

| Compound | Structure | T-type $IC_{50}$ ($\mu$M)[a] | L-type $IC_{50}$ ($\mu$M)[b] | Selectivity (L/T) |
|---|---|---|---|---|
| Mibefradil (**1**) |  | 0.20 | 1.1 | 5.5 |
| **2** |  | 0.089 | 4.4 | 49 |
| **3** |  | 0.076 | 2.2 | 29 |
| **4a** |  | 0.062 | 10 | 161 |

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




Reagents and conditions: (a) [1-(Boc)piperidin-4-yl]acetic acid, WSCD, HOBt, $Et_3N$, $CH_3CN$; (b) HCl, AcOEt; (c) aldehyde, $NaBH(OAc)_3$, AcOH, $CH_2Cl_2$ (Method A) or alkyl–OTs, $K_2CO_3$, $CH_3CN$ (Method B)

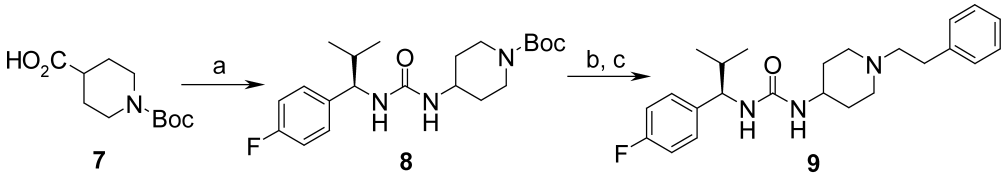
Chart 1

cally active amine **5**[44] with [1-(*tert*-butoxycarbonyl(Boc)) piperidin-4-yl]acetic acid in the presence of 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (WSCD) and 1-hydroxybenzotriazole (HOBt) followed by deprotection of the Boc group with hydrogen chloride gave key intermediate **6**. Alkylation of piperidine **6** was carried out *via* two general methods, A and B. In Method A, compounds **4a**—**e** were synthesized by reductive amination of **6** with the corresponding aldehydes. In Method B, compounds **4f**—**j** were prepared by alkylation of **6** with the corresponding tosylates under basic conditions.

A compound bearing a urea junction (**9**) was synthesized as shown in Chart 2. The Curtius rearrangement of carboxylic acid **7** followed by reaction with amine **5** yielded urea **8**. Deprotection and alkylation of the piperidine moiety afforded compound **9**.

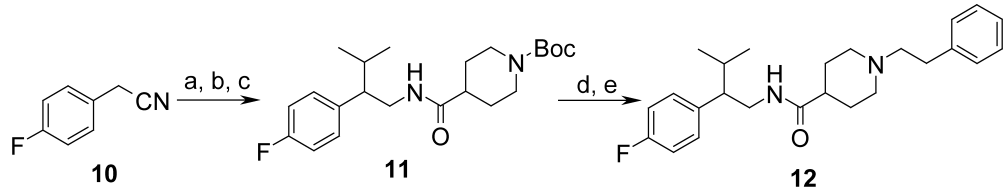
Chart 3 shows the synthesis of **12**, which contained an amide junction at a different position compared with **4a**. 4-Fluorophenylacetonitrile (**10**) was transformed to compound **11** in a three-step sequence involving alkylation of the benzylic position, hydrogenation of the nitrile group in the presence of Raney–Ni, and condensation with 1-(Boc)piperidine-4-carboxylic acid. Deprotection and alkylation of the piperidine generated compound **12**.

The synthesis of various phenethyl tosylates is illustrated in Chart 4. Commercially available phenethyl alcohol **13** was transformed to **14** by alkylation with 2-methoxyethyl bromide and tosylation. 3- and 5-fluoro derivatives (**17a**, **b**) were prepared by allylation of phenols **15a**, **b**, Claisen rearrangement under thermal conditions, and alkylation of the phenol moiety to afford **16a**, **b**. After oxidative cleavage of olefin followed by reduction with sodium borohydride, tosylation of the corresponding alcohols produced **17a**, **b**. 4-Fluoro derivative **20** was obtained from commercially available carboxylic acid **18**. Compound **18** was converted into benzaldehyde **19** in a four-step sequence, involving esterification under acidic conditions, alkylation, reduction of the ester with $LiAlH_4$, and re-oxidation with $MnO_2$. Transformation of the benzaldehyde



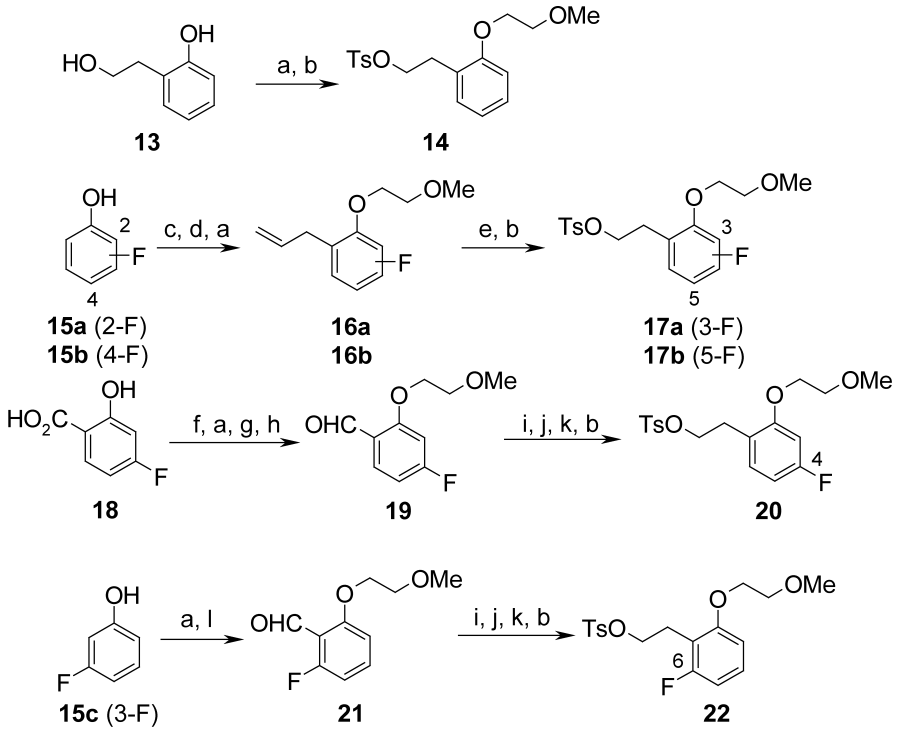
Reagents and conditions: (a) diphenylphosphoryl azide, $Et_3N$, PhMe, reflux then **5**, $Et_3N$, DMF; (b) HCl, AcOEt; (c) phenylacetaldehyde, $NaBH(OAc)_3$, AcONa, $CH_2Cl_2$.

Chart 2



Reagents and conditions: (a) NaH, iPrBr, DMF, PhMe; (b) $H_2$, Raney–Ni, $NH_4OH$, EtOH; (c) 1-(Boc)piperidine-4-carboxylic acid, WSCD, HOBt, DMF; (d) HCl, AcOEt; (e) phenylacetaldehyde, $NaBH(OAc)_3$, AcONa, $CH_2Cl_2$.

Chart 3



Reagents and conditions: (a) 2-methoxyethyl bromide, $K_2CO_3$, DMF; (b) TsCl, Py; (c) allyl bromide, $K_2CO_3$, acetone; (d) *o*-di$Cl_2C_6H_4$, reflux; (e) $O_3$, $CHCl_3$, EtOH then $NaBH_4$; (f) $H_2SO_4$, MeOH; (g) $LiAlH_4$, THF; (h) $MnO_2$, $CHCl_3$; (i) $Ph_3P^+CH_2OMeCl^-$, *t*BuOK, THF; (j) $HCO_2H$; (k) $NaBH_4$, EtOH; (l) BuLi, THF then DMF.

Chart 4

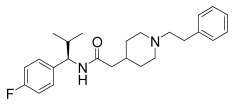
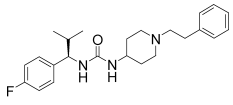
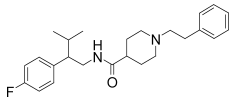
moiety in **19** to phenethyl tosylate was accomplished by the Wittig reaction, treatment with formic acid, reduction with $NaBH_4$, and tosylation. 6-Fluoro derivative **22** was synthesized as follows. After alkylation of 3-fluorophenol (**15c**), the resulting compound was subjected to regioselective lithiation and subsequent formylation to give benzaldehyde **21**. Compound **21** was converted to 6-fluoro phenethyl tosylate **22** in the same manner as described for **20**.

## Results and Discussion

We first investigated the effects of modifying the tether between the 1-(4-fluorophenyl)-2-methylpropyl moiety and piperidine of **4a** on T- and L-type $Ca^{2+}$ channel inhibitory activity (Table 2). Replacement of the amide with urea (**9**) dramatically reduced the inhibitory activity against T-type $Ca^{2+}$ channels, while transformation of 2-(piperidin-4-yl)acetamide to piperidine-4-carboxamide (**12**) resulted in 3-fold decreased activity compared to **4a**. These results suggested that the functionality of the amide as a tether was suitable and that the position of the amide played an important role in the inhibitory activity of this compound against T-type $Ca^{2+}$ channels. With regard to the selectivity of T- *versus* L-type $Ca^{2+}$ channels, **4a** exhibited superior selectivity for T-type channels to the other tested compounds. Therefore, we selected compound **4a** for further optimization.

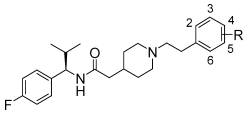
We next modified the pendant benzene ring of the pheneth-

Table 2. $Ca^{2+}$ Channel Blocking Activity of Piperidine Derivatives (**4a**, **9**, **12**)

| Compound | Structure | T-type $IC_{50}$ ($\mu$M)[a] | L-type $IC_{50}$ ($\mu$M)[b] | Selectivity (L/T) |
|---|---|---|---|---|
| **4a** |  | 0.062 | 10 | 161 |
| **9** |  | 2.0 | 5.0 | 2.5 |
| **12** |  | 0.21 | 3.9 | 19 |

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

Table 3. $Ca^{2+}$ Channel Blocking Activity of *N*-[(1*R*)-1-(4-Fluorophenyl)-2-methylpropyl]-1-(1-phenethylpiperidin-4-yl)acetamide Derivatives (**4a**—**4j**)



| Compound | R | T-type $IC_{50}$ ($\mu$M)[a] | L-type $IC_{50}$ ($\mu$M)[b] | Selectivity (L/T) |
|---|---|---|---|---|
| **4a** | R=H | 0.062 | 10 | 161 |
| **4b** | R=2-OMe | 0.16 | 6.8 | 43 |
| **4c** | R=3-OMe | 0.20 | 7.0 | 35 |
| **4d** | R=4-OMe | 0.24 | 45%[c] | >42 |
| **4e** | R=3,4-diOMe | 0.30 | 40%[c] | >33 |
| **4f** | R=2-$OCH_2CH_2OMe$ | 0.19 | 38%[c] | >53 |
| **4g** | R=3-F-2-$OCH_2CH_2OMe$ | 0.42 | 2.1 | 5.0 |
| **4h** | R=4-F-2-$OCH_2CH_2OMe$ | 0.31 | 1.9 | 6.1 |
| **4i** | R=5-F-2-$OCH_2CH_2OMe$ | 0.31 | 3.1 | 10 |
| **4j** | R=6-F-2-$OCH_2CH_2OMe$ | 0.26 | 3.1 | 12 |

*a*) Inhibition of $Ca^{2+}$ influx through T-type $Ca^{2+}$ channels. See Experimental. *b*) Inhibition of $Ca^{2+}$ influx through L-type $Ca^{2+}$ channels. See Experimental. *c*) % inhibition @10$\mu$M.

yl side chain of **4a** (Table 3). As we have previously reported that the introduction of an electron-donating substituent enhanced the inhibitory activity against T-type $Ca^{2+}$ channels,[44] here, we introduced methoxy groups into **4a**. In this series of derivatives, however, the introduction of methoxy groups slightly reduced the inhibitory activity compared to the parent compound (**4a**), with the compound bearing 3,4-diMeO substituents (**4e**) showing less potent activity than the mono-substituted derivatives. As the 2-MeO derivative (**4b**) exhibited the most potent activity, the modification of the methoxy moiety of **4b** was performed. The introduction of a 2-methoxyethoxy group (**4f**) at the 2-position of the pendant benzene ring retained the inhibitory activity and exhibited good selectivity for T-type $Ca^{2+}$ channels over L-type $Ca^{2+}$ channels. To obtain a compound with more potent inhibitory activity against T-type $Ca^{2+}$ channels, the benzene ring of **4f** was further modified by the introduction of an additional substituent. All compounds with an additional fluorine atom (**4g**—**j**) showed equipotent inhibitory activities towards T-type $Ca^{2+}$ channels; however, these compounds also displayed moderate inhibitory activities against L-type $Ca^{2+}$ channels.

Based on these findings, we selected compounds **4a**, **b**, and **f** for the evaluation of bradycardic activity in isolated guinea pig right atria (Table 4). Compound **4a** was found to exert potent bradycardic activity, with an $EC_{30}$ value of 2.3$\mu$M, which was equipotent to that of mibefradil ($EC_{30}$=2.9$\mu$M). The introduction of an electron donating substituent into **4a** enhanced the bradycardic activities, particularly for **4f**, which exhibited the most potent bradycardic activity, with an $EC_{30}$ value of 0.59$\mu$M.

Table 4. Bradycardic Activity of Selected Compounds (**1**, **4a**,**b**,**f**)

| Compound | $EC_{30}$ ($\mu$M)[a] |
|---|---|
| Mibefradil (**1**) | 2.9 |
| **4a** | 2.3 |
| **4b** | 1.5 |
| **4f** | 0.59 |

*a*) See Experimental.

Given its potent inhibitory activity against T-type $Ca^{2+}$ channels and the bradycardic activity observed in isolated guinea pig right atria, compound **4f** was subjected to further pharmacological evaluations. Oral administration of **4f** at

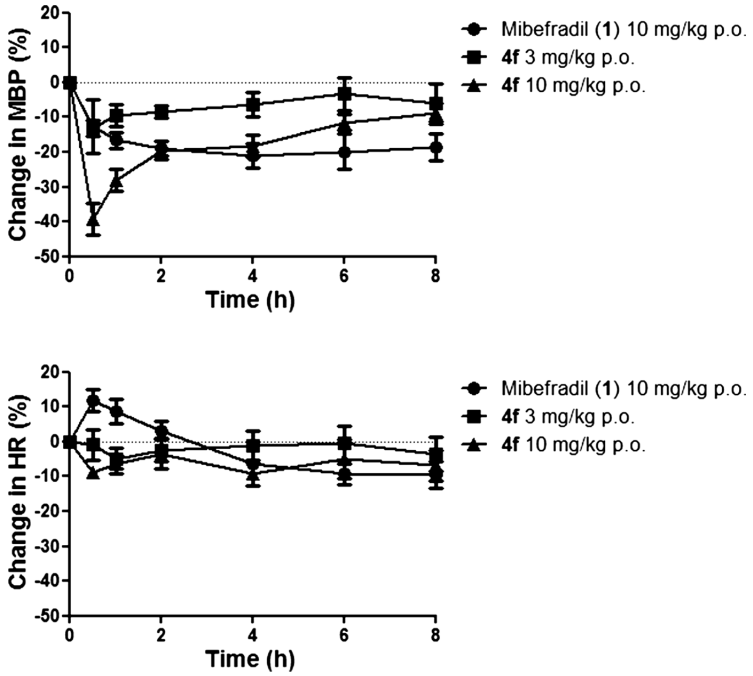



Fig. 1. Effects of **4f** and Mibefradil (**1**) on Mean Blood Pressure (MBP) and Heart Rate (HR) in Conscious Spontaneously Hypertensive Rats
The compounds were orally administered at 0 h. The values are presented as the means±standard error of the mean from at least four experiments.

Table 5. Inhibitory Activity of **1** and **4f** against $Ca^{2+}$ Currents[a]

| Compound | $I_{Ca\text{-}T}$ $IC_{50}$ ($\mu$M) | $I_{Ca\text{-}L}$ $IC_{50}$ ($\mu$M) | Selectivity (L/T) |
|---|---|---|---|
| Mibefradil (**1**) | 0.12 | 3.2 | 27 |
| **4f** | 0.18 | 38 | 212 |

*a*) See Experimental.

10 mg/kg to spontaneously hypertensive rats induced a 39% reduction of mean blood pressure (Fig. 1), and the effect was sustained for more than 8 h. Notably, reflex tachycardia was not observed in rats despite the potent antihypertensive activity of this compound. In contrast, mibefradil showed slight reflex tachycardia (12% increase in HR), which was likely due to insufficient T-type selectivity (L/T=5.5). In addition, the magnitude of blood pressure lowering induced by **4f** was greater than that induced by mibefradil (21%). The hypotensive effect induced by **4f** was caused by the blockage of T-type $Ca^{2+}$ channels, because **4f** displayed little inhibitory activity against L-type $Ca^{2+}$ channels.

Finally, we examined the effects of **4f** on T-type $Ca^{2+}$ currents in HEK293 cells stably expressing human $Ca_v3.1$ ($\alpha$1G) using a whole-cell patch clamp technique. In this system, compound **4f** inhibited T-type $Ca^{2+}$ currents with an $IC_{50}$ value of 0.18 $\mu$M, which was equipotent to that of mibefradil ($IC_{50}$=0.12 $\mu$M). However, **4f** showed poor inhibitory activity against L-type $Ca^{2+}$ currents, with an $IC_{50}$ value of 38 $\mu$M, which was 10-fold less potent than that of mibefradil ($IC_{50}$=3.2 $\mu$M).

To our knowledge, this study represents the first report of a selective T-type $Ca^{2+}$ channel blocker that induces antihypertensive effects after oral administration.[45] These results indicate that the potent antihypertensive effect of **4f** is associated with the direct inhibition of T-type $Ca^{2+}$ channels.

## Conclusion

We synthesized and evaluated a series of 2-(1-alkylpiperidin-4-yl)-*N*-[(1*R*)-1-(4-fluorophenyl)-2-methylpropyl]acetamide derivatives and found that *N*-[(1*R*)-1-(4-fluorophenyl)-2-methylpropyl]-2-(1-{2-[2-(2-methoxyethoxy)phenyl]ethyl}-piperidin-4-yl)acetamide (**4f**) showed potent and specific inhibition of T-type $Ca^{2+}$ channels. Compound **4f** exerted an antihypertensive effect without associated reflex tachycardia when orally administered to spontaneously hypertensive rats. Together, these data reveal for the first time that the selective inhibition of T-type $Ca^{2+}$ channels induces vasodilation. Therefore, we propose that **4f** may be a useful compound to further explore the pharmacological profile of this novel class of T-type selective $Ca^{2+}$ channel inhibitors as antihypertensive agents.

## Experimental

$^1$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; dt, double triplet; 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).

***N*-[(1*R*)-1-(4-Fluorophenyl)-2-methylpropyl]-2-(piperidin-4-yl)acetamide (6)** To an ice-cooled mixture of **5**[44] (6.1 g, 29.9 mmol), $Et_3N$ (10 mL, 71.7 mmol), [1-(Boc)piperidin-4-yl]acetic acid (7.34 g, 30.2 mmol), and HOBt (4.2 g, 30.4 mmol) in $CH_3CN$ (100 mL) was added WSCD (6.0 g, 31.4 mmol) and the mixture was stirred at room temperature for 2 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-(2-{[(*1R*)-1-(4-fluorophenyl)-2-methylpropyl]amino}-2-oxoethyl)piperidine-1-carboxylate (11.8 g) as a colorless foam. To an ice-cooled solution of the *N*-Boc derivative obtained above (11.8 g) in AcOEt (50 mL) was added 4 M HCl–AcOEt (50 mL, 200 mmol) and the mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated *in vacuo* and partitioned between $CHCl_3$ and aqueous potassium carbonate solution. The organic layer was washed with brine, dried over $Na_2SO_4$, and evaporated *in vacuo* to give the title compound **6** (8.54 g, 2 steps 98%) as a colorless solid.

$^1$H-NMR ($CDCl_3$) $\delta$: 0.82 (3H, d, $J$=6.8 Hz), 0.96 (3H, d, $J$=6.8 Hz), 1.05—1.19 (2H, m), 1.54—1.74 (2H, m), 1.85—2.05 (2H, m), 2.09 (2H, d, $J$=7.2 Hz), 2.56—2.65 (2H, m), 2.97—3.07 (2H, m), 4.72 (1H, dd, $J$=8.4, 8.4 Hz), 5.69 (1H, d, $J$=8.4 Hz), 7.00 (2H, dd, $J$=8.4, 8.8 Hz), 7.19 (2H, dd, $J$=5.2, 8.8 Hz). MS (FAB) *m/z*: 293 ($M^+$+1).

***N*-[(1*R*)-1-(4-Fluorophenyl)-2-methylpropyl]-2-[1-(2-phenylethyl)piperidin-4-yl]acetamide Oxalate (4a) (Method A)** To an ice-cooled mixture of **6** (0.45 g, 1.54 mmol), phenylacetaldehyde (0.26 g, 2.16 mmol), and acetic acid (0.3 mL) in $CH_2Cl_2$ (10 mL) was added sodium triacetoxyborohydride (0.60 g, 2.83 mmol) and the mixture was stirred at room temperature for 25 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*-[(1*R*)-1-(4-fluorophenyl)-2-methylpropyl]-2-[1-(2-phenylethyl)piperidin-4-yl]acetamide (0.60 g) as a colorless solid. The compound was converted to its oxalate by treating it with oxalic acid (0.14 g, 1.55 mmol). The crude salt was suspended with $CH_3CN$ and filtered to give the title compound **4a** (0.37 g, 49%) as a colorless powder.

$^1$H-NMR (DMSO-$d_6$) $\delta$: 0.70 (3H, d, $J$=6.4 Hz), 0.89 (3H, d, $J$=6.4 Hz), 1.35—1.53 (2H, m), 1.62—1.82 (2H, m), 1.83—1.97 (2H, m), 2.06—2.18 (2H, m), 2.76—2.91 (2H, m), 2.91—3.00 (2H, m), 3.09—3.20 (2H, m), 3.36—3.50 (2H, m), 4.54 (1H, dd, $J$=8.8, 8.8 Hz), 7.13 (2H, dd, $J$=7.6, 8.0 Hz), 7.22—7.36 (7H, m), 8.30 (1H, d, $J$=8.8 Hz). MS (FAB) *m/z*: 397 ($M^+$+1). *Anal.* Calcd for $C_{25}H_{33}N_2OF{\cdot}C_2H_2O_4$: C, 66.65; H, 7.25; N, 5.76; F, 3.90. Found: C, 66.60; H, 7.24; N, 5.74; F, 3.94.

***N*-[(1*R*)-1-(4-Fluorophenyl)-2-methylpropyl]-2-{1-[2-(2-methoxyphenyl)ethyl]piperidin-4-yl}acetamide Oxalate (4b)** The title compound was prepared in the same manner as described for **4a** using 2-methoxyphenylacetaldehyde instead of phenylacetaldehyde, in 72% yield.

$^1$H-NMR (DMSO-$d_6$) $\delta$: 0.70 (3H, d, $J$=6.8 Hz), 0.89 (3H, d, $J$=6.8 Hz), 1.35—1.53 (2H, m), 1.62—1.82 (2H, m), 1.83—1.98 (2H, m), 2.06—2.19 (2H, m), 2.80—2.98 (4H, m), 3.03—3.12 (2H, m), 3.37—3.50 (2H, m), 3.79 (3H, s), 4.54 (1H, dd, $J$=8.8, 8.8 Hz), 6.90 (1H, dd, $J$=7.6, 8.0 Hz), 6.99 (1H, d, $J$=8.0 Hz), 7.09—7.20 (3H, m), 7.22—7.33 (3H, m), 8.32 (1H, d, $J$=8.8 Hz). MS (FAB) *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, 64.99; H, 7.29; N, 5.43; F, 3.68.

***N*-[(1*R*)-1-(4-Fluorophenyl)-2-methylpropyl]-2-{1-[2-(3-methoxyphenyl)ethyl]piperidin-4-yl}acetamide Oxalate (4c)** The title compound was prepared in the same manner as described for **4a** using 3-methoxyphenylacetaldehyde instead of phenylacetaldehyde, in 71% yield.

$^1$H-NMR (DMSO-$d_6$) $\delta$: 0.70 (3H, d, $J$=6.8 Hz), 0.89 (3H, d, $J$=6.8 Hz), 1.36—1.53 (2H, m), 1.62—1.82 (2H, m), 1.83—1.96 (2H, m), 2.06—2.18 (2H, m), 2.77—2.98 (4H, m), 3.10—3.20 (2H, m), 3.36—3.48 (2H, m), 3.74 (3H, s), 4.54 (1H, dd, $J$=8.8, 9.2 Hz), 6.78—6.85 (3H, m), 7.13 (2H, dd, $J$=7.6, 8.0 Hz), 7.20—7.32 (3H, m), 8.31 (1H, d, $J$=9.2 Hz). MS (FAB) *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, 64.99; H, 7.22; N, 5.39; F, 3.70.

***N*-[(1*R*)-1-(4-Fluorophenyl)-2-methylpropyl]-2-{1-[2-(4-methoxyphenyl)ethyl]piperidin-4-yl}acetamide Oxalate (4d)** The title compound was prepared in the same manner as described for **4a** using 4-methoxyphenylacetaldehyde instead of phenylacetaldehyde, in 74% yield.

$^1$H-NMR (DMSO-$d_6$) $\delta$: 0.70 (3H, d, $J$=6.8 Hz), 0.88 (3H, d, $J$=6.8 Hz), 1.36—1.51 (2H, m), 1.62—1.82 (2H, m), 1.83—1.96 (2H, m), 2.06—2.18 (2H, m), 2.77—2.94 (4H, m), 3.05—3.15 (2H, m), 3.35—3.48 (2H, m), 3.72 (3H, s), 4.54 (1H, dd, $J$=8.4, 8.8 Hz), 6.89 (2H, d, $J$=8.8 Hz), 7.09—7.19 (4H, m), 7.29 (2H, dd, $J$=5.6, 8.4 Hz), 8.30 (1H, d, $J$=8.8 Hz). MS (FAB) *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, 65.11; H, 7.30; N, 5.38; F, 3.70.

**2-{1-[2-(3,4-Dimethoxyphenyl)ethyl]piperidin-4-yl}-*N*-[(1*R*)-1-(4-fluorophenyl)-2-methylpropyl]acetamide Oxalate (4e)** The title compound was prepared in the same manner as described for **4a** using 3,4-dimethoxyphenylacetaldehyde instead of phenylacetaldehyde, in 48% yield.

$^1$H-NMR (DMSO-$d_6$) $\delta$: 0.70 (3H, d, $J$=6.8 Hz), 0.89 (3H, d, $J$=6.8 Hz), 1.36—1.52 (2H, m), 1.62—1.82 (2H, m), 1.82—1.96 (2H, m), 2.06—2.18 (2H, m), 2.77—2.93 (4H, m), 3.08—3.18 (2H, m), 3.35—3.49 (2H, m), 3.72 (3H, s), 3.74 (3H, s), 4.54 (1H, dd, $J$=8.8, 9.2 Hz), 6.75 (1H, dd, $J$=1.6, 8.0 Hz), 6.84—6.91 (2H, m), 7.13 (2H, dd, $J$=8.4, 8.8 Hz), 7.29 (2H, dd, $J$=5.6, 8.4 Hz), 8.31 (1H, d, $J$=9.2 Hz). MS (FAB) *m/z*: 457 ($M^+$+1). *Anal.* Calcd for $C_{27}H_{37}N_2O_3F{\cdot}C_2H_2O_4$: C, 63.72; H, 7.19; N, 5.12; F, 3.48. Found: C, 63.62; H, 7.23; N, 5.11; F, 3.51.

***N*-[(1*R*)-1-(4-Fluorophenyl)-2-methylpropyl]-2-(1-{2-[2-(2-methoxyethoxy)phenyl]ethyl}piperidin-4-yl)acetamide Hydrochloride (4f) (Method B)** To a mixture of **6** (7.80 g, 26.7 mmol) and $K_2CO_3$ (6.0 g, 43.4 mmol) in $CH_3CN$ (100 mL) was added **14** (10.7 g, 30.5 mmol) and the mixture was stirred at 50°C for 20 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 (MeOH/$CHCl_3$=5/95) to give *N*-[(1*R*)-1-(4-fluorophenyl)-2-methylpropyl]-2-(1-{2-[2-(2-methoxyethoxy)phenyl]ethyl}-piperidin-4-yl)acetamide (12.4 g) as a colorless solid. The compound was converted to its hydrochloride salt by treating it with 4 M HCl–AcOEt (7.0 mL, 28.0 mmol). The crude salt was suspended with $CH_3CN$ and filtered to give the title compound **4f** (10.93 g, 81%) as a colorless powder.

$[\alpha]_D^{25}$ +46.50 ($c$=1.00, MeOH). $^1$H-NMR (DMSO-$d_6$) $\delta$: 0.70 (3H, d, $J$=6.8 Hz), 0.89 (3H, d, $J$=6.8 Hz), 1.48—1.82 (4H, m), 1.84—1.98 (2H, m), 2.07—2.18 (2H, m), 2.82—3.04 (4H, m), 3.06—3.16 (2H, m), 3.31 (3H, s), 3.42—3.53 (2H, m), 3.67—3.73 (2H, m), 4.08—4.15 (2H, m), 4.54 (1H, dd, $J$=8.4, 8.8 Hz), 6.91 (1H, dd, $J$=7.2, 7.6 Hz), 7.00 (1H, d, $J$=7.6 Hz), 7.13 (2H,

dd, *J*=8.4, 8.8 Hz), 7.17—7.27 (2H, m), 7.30 (2H, dd, *J*=5.6, 8.4 Hz), 8.38 (1H, d, *J*=8.8 Hz), 10.45 (1H, brs). MS (FAB) *m/z*: 471 ($M^+$+1). *Anal.* Calcd for $C_{28}H_{39}N_2O_3F$·HCl: C, 66.32; H, 7.95; N, 5.52; Cl, 6.99; F, 3.75. Found: C, 66.20; H, 8.03; N, 5.54; Cl, 7.05; F, 3.76.

**2-(1-{2-[3-Fluoro-2-(2-methoxyethoxy)phenyl]ethyl}-piperidin-4-yl)-*N*-[(1*R*)-1-(4-fluorophenyl)-2-methylpropyl]-acetamide Oxalate (4g)** The title compound was prepared in the same manner as described for **4f** using **17a** instead of **14**, in 56% yield.

$^1$H-NMR (DMSO-$d_6$) $\delta$: 0.70 (3H, d, *J*=6.8 Hz), 0.89 (3H, d, *J*=6.8 Hz), 1.36—1.54 (2H, m), 1.62—1.82 (2H, m), 1.84—1.97 (2H, m), 2.07—2.18 (2H, m), 2.77—2.94 (2H, m), 2.96—3.05 (2H, m), 3.05—3.14 (2H, m), 3.29 (3H, s), 3.35—3.48 (2H, m), 3.59—3.65 (2H, m), 4.12—4.18 (2H, m), 4.54 (1H, dd, *J*=8.4, 8.8 Hz), 7.02—7.20 (5H, m), 7.30 (2H, dd, *J*=5.6, 8.4 Hz), 8.31 (1H, d, *J*=8.8 Hz). MS (FAB) *m/z*: 489 ($M^+$+1). *Anal.* Calcd for $C_{28}H_{38}N_2O_3F_2·C_2H_2O_4$: C, 62.27; H, 6.97; N, 4.84; F, 6.57. Found: C, 62.21; H, 6.93; N, 4.80; F, 6.62.

**2-(1-{2-[4-Fluoro-2-(2-methoxyethoxy)phenyl]ethyl}-piperidin-4-yl)-*N*-[(1*R*)-1-(4-fluorophenyl)-2-methylpropyl]-acetamide Hydrochloride (4h)** The title compound was prepared in the same manner as described for **4f** using **20** instead of **14**, in 59% yield.

$^1$H-NMR (DMSO-$d_6$) $\delta$: 0.70 (3H, d, *J*=6.8 Hz), 0.89 (3H, d, *J*=6.8 Hz), 1.50—1.82 (4H, m), 1.84—1.98 (2H, m), 2.06—2.19 (2H, m), 2.81—3.01 (4H, m), 3.03—3.13 (2H, m), 3.31 (3H, s), 3.40—3.51 (2H, m), 3.67—3.73 (2H, m), 4.11—4.16 (2H, m), 4.55 (1H, dd, *J*=8.4, 8.8 Hz), 6.74 (1H, ddd, *J*=2.4, 8.4, 8.4 Hz), 6.93 (1H, dd, *J*=2.4, 11.2 Hz), 7.13 (2H, dd, *J*=8.4, 8.8 Hz), 7.22 (1H, dd, *J*=7.2, 8.4 Hz), 7.31 (2H, dd, *J*=5.6, 8.4 Hz), 8.39 (1H, d, *J*=8.8 Hz), 10.59 (1H, brs). MS (FAB) *m/z*: 489 ($M^+$+1). *Anal.* Calcd for $C_{28}H_{38}N_2O_3F_2$·HCl: C, 64.05; H, 7.49; N, 5.34; Cl, 6.75; F, 7.24. Found: C, 63.94; H, 7.59; N, 5.31; Cl, 6.70; F, 7.22.

**2-(1-{2-[5-Fluoro-2-(2-methoxyethoxy)phenyl]ethyl}-piperidin-4-yl)-*N*-[(1*R*)-1-(4-fluorophenyl)-2-methylpropyl]-acetamide Hydrochloride (4i)** The title compound was prepared in the same manner as described for **4f** using **17b** instead of **14**, in 23% yield.

$^1$H-NMR (DMSO-$d_6$) $\delta$: 0.70 (3H, d, *J*=6.8 Hz), 0.89 (3H, d, *J*=6.8 Hz), 1.49—1.82 (4H, m), 1.84—1.98 (2H, m), 2.08—2.19 (2H, m), 2.82—2.95 (2H, m), 2.95—3.15 (2H, m), 3.09—3.18 (2H, m), 3.31 (3H, s), 3.38—3.52 (2H, m), 3.65—3.71 (2H, m), 4.07—4.14 (2H, m), 4.54 (1H, dd, *J*=8.4, 8.8 Hz), 6.99—7.16 (5H, m), 7.31 (2H, dd, *J*=5.6, 8.4 Hz), 8.38 (1H, d, *J*=8.8 Hz), 10.54 (1H, brs). MS (FAB) *m/z*: 489 ($M^+$+1). *Anal.* Calcd for $C_{28}H_{38}N_2O_3F_2$·HCl·$H_2O$: C, 61.92; H, 7.61; N, 5.16; Cl, 6.53; F, 7.00. Found: C, 62.00; H, 7.65; N, 4.93; Cl, 6.43; F, 6.91.

**2-(1-{2-[6-Fluoro-2-(2-methoxyethoxy)phenyl]ethyl}-piperidin-4-yl)-*N*-[(1*R*)-1-(4-fluorophenyl)-2-methylpropyl]-acetamide Hydrochloride (4j)** The title compound was prepared in the same manner as described for **4f** using **22** instead of **14**, in 85% yield.

$^1$H-NMR (DMSO-$d_6$) $\delta$: 0.70 (3H, d, *J*=6.8 Hz), 0.89 (3H, d, *J*=6.8 Hz), 1.54—1.82 (4H, m), 1.83—1.99 (2H, m), 2.06—2.20 (2H, m), 2.82—2.97 (2H, m), 3.05 (4H, brs), 3.31 (3H, s), 3.44—3.56 (2H, m), 3.68—3.75 (2H, m), 4.12—4.19 (2H, m), 4.55 (1H, dd, *J*=8.4, 8.8 Hz), 6.82 (1H, dd, *J*=8.0, 8.4 Hz), 6.88 (1H, d, *J*=8.0 Hz), 7.13 (2H, dd, *J*=8.4, 8.8 Hz), 7.23—7.35 (3H, m), 8.42 (1H, d, *J*=8.8 Hz), 10.76 (1H, brs). MS (FAB) *m/z*: 489 ($M^+$+1). *Anal.* Calcd for $C_{28}H_{38}N_2O_3F_2$·HCl·0.7$H_2O$: C, 62.55; H, 7.57; N, 5.21; Cl, 6.59; F, 7.07. Found: C, 62.49; H, 7.78; N, 5.15; Cl, 6.59; F, 7.07.

***tert*-Butyl 4-({[(1*R*)-1-(4-Fluorophenyl)-2-methylpropyl]-carbamoyl}amino)piperidine-1-carboxylate (8)** To a mixture of **7** (2.0 g, 8.72 mmol) and $Et_3N$ (1.5 mL, 10.8 mmol) in PhMe (30 mL) was added diphenylphosphoryl azide (2.0 mL, 9.28 mmol) and the mixture was stirred at room temperature for 3 h. The mixture was poured onto aqueous sodium bicarbonate solution and then extracted with PhMe. The organic layer was washed with brine, dried over $Na_2SO_4$, and evaporated *in vacuo* to give *tert*-butyl 4-(azidocarbonyl)piperidine-1-carboxylate (2.2 g, 99%) as a brown oil. A mixture of the acylazide obtained above (2.2 g, 8.65 mmol) in PhMe (10 mL) was stirred at 120°C for 1.5 h. The reaction mixture was concentrated *in vacuo* to give *tert*-butyl 4-isocyanatopiperidine-1-carboxylate (2.0 g, quantitative) as a brown oil. To an ice-cooled mixture of **5** (0.60 g, 2.95 mmol) and $Et_3N$ (1.0 mL, 7.17 mmol) in *N*,*N*-dimethylformamide (DMF) (10 mL) was added isocyanate obtained above (1.0 g, 4.36 mmol) and the mixture was stirred at room temperature for 24 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=1/1) to give the title compound (0.95 g, 82%) as a colorless foam.

$^1$H-NMR ($CDCl_3$) $\delta$: 0.83 (3H, d, *J*=6.8 Hz), 0.95 (3H, d, *J*=6.8 Hz), 1.01—1.09 (1H, m), 1.11—1.23 (1H, m), 1.44 (9H, s), 1.71—1.88 (2H, m), 1.88—1.98 (1H, m), 2.75—2.87 (2H, m), 3.62—3.74 (1H, m), 3.80—3.96 (2H, m), 4.03 (1H, d, *J*=7.6 Hz), 4.31 (1H, dd, *J*=6.8, 7.2 Hz), 4.62 (1H, d, *J*=6.8 Hz), 7.02 (2H, dd, *J*=8.4, 8.8 Hz), 7.21 (2H, dd, *J*=5.2, 8.8 Hz). MS (FAB) *m/z*: 394 ($M^+$+1).

**1-[(1*R*)-1-(4-Fluorophenyl)-2-methylpropyl]-3-[1-(2-phenylethyl)piperidin-4-yl]urea Oxalate (9)** To an ice-cooled solution of **8** (0.95 g, 2.14 mmol) in AcOEt (5.0 mL) was added 4 M HCl–AcOEt (5.0 mL, 20.0 mmol) and the mixture was stirred at room temperature for 18 h. The reaction mixture was concentrated *in vacuo* and the resulting solid was used for the next step without further purification. To an ice-cooled mixture of the piperidine derivative obtained above (0.42 g, 1.27 mmol), sodium acetate (0.13 g, 1.58 mmol) and phenylacetaldehyde (0.22 g, 1.83 mmol) in $CH_2Cl_2$ (10 mL) was added sodium triacetoxyborohydride (0.54 g, 2.54 mmol) and the mixture was stirred at room temperature for 3 d. 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-[(1*R*)-1-(4-fluorophenyl)-2-methylpropyl]-3-[1-(2-phenylethyl) piperidin-4-yl]urea (0.50 g) as a colorless solid. The compound was converted to its oxalate by treating it with oxalic acid (0.11 g, 1.22 mmol). The crude salt was suspended with $CH_3CN$ and filtered to give the title compound **9** (0.35 g, 57%) as a colorless powder.

$^1$H-NMR (DMSO-$d_6$) $\delta$: 0.76 (3H, d, *J*=6.8 Hz), 0.81 (3H, d, *J*=6.8 Hz), 1.52—1.70 (2H, m), 1.81—2.01 (3H, m), 2.90—3.02 (4H, m), 3.12—3.21 (2H, m), 3.39 (2H, brs), 3.58 (1H, brs), 4.45 (1H, dd, *J*=7.2, 8.8 Hz), 6.23 (1H, brs), 6.46 (1H, d, *J*=8.8 Hz), 7.12 (2H, dd, *J*=8.4, 8.8 Hz), 7.21—7.29 (5H, m),

7.33 (2H, dd, *J*=5.2, 8.8 Hz). MS (FAB) *m/z*: 398 ($M^+$+1). *Anal.* Calcd for $C_{24}H_{32}N_3OF \cdot C_2H_2O_4$: C, 64.05; H, 7.03; N, 8.62; F, 3.90. Found: C, 64.21; H, 7.20; N, 8.74; F, 3.98.

***tert*-Butyl 4-{[2-(4-Fluorophenyl)-3-methylbutyl]carbamoyl}piperidine-1-carboxylate (11)** To a mixture of sodium hydride (60% dispersion in mineral oil; 0.65 g, 16.3 mmol) and isopropyl bromide (2.0 mL, 21.3 mmol) in DMF (2.0 mL) and PhMe (10 mL) was added a solution of **10** (2.0 g, 14.8 mmol) in PhMe (10 mL) at 70°C and the mixture was stirred at 90°C 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=1/30) to give 2-(4-fluorophenyl)-3-methylbutanenitrile (1.85 g, 71%) as a colorless oil. To a suspension of Raney–Ni (*ca.* 2.0 g) and 28 w/w% $NH_4OH$ (2.0 mL) in EtOH (15 mL) was added the nitrile obtained above (1.85 g, 10.4 mmol) and the mixture was stirred under hydrogen atmosphere at room temperature for 15 h. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to give 2-(4-fluorophenyl)-3-methylbutan-1-amine (1.9 g, quantitative) as a light yellow oil. To an ice-cooled mixture of the amine obtained above (1.9 g, 10.5 mmol), 1-(Boc)piperidine-4-carboxylic acid (2.6 g, 11.3 mmol), and HOBt (1.5 g, 11.1 mmol) in DMF (20 mL) was added WSCD (2.2 g, 11.5 mmol) and the mixture was stirred at room temperature for 24 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 **11** (3.98 g, 97%) as a colorless foam.

$^1$H-NMR ($CDCl_3$) $\delta$: 0.72 (3H, d, *J*=6.8 Hz), 1.01 (3H, d, *J*=6.8 Hz), 1.39—1.50 (11H, m), 1.54—1.62 (2H, m), 1.77—1.87 (1H, m), 1.96—2.05 (1H, m), 2.46—2.54 (1H, m), 2.58—2.70 (2H, m), 3.17—3.25 (1H, m), 3.86—3.94 (1H, m), 3.97—4.11 (2H, m), 5.09 (1H, br s), 7.02 (2H, dd, *J*=8.4, 8.8 Hz), 7.09 (2H, dd, *J*=5.2, 8.8 Hz). MS (FAB) *m/z*: 393 ($M^+$+1).

***N*-[2-(4-Fluorophenyl)-3-methylbutyl]-1-(2-phenylethyl)-piperidine-4-carboxamide Hydrochloride (12)** The title compound was prepared in the same manner as described for **9** using **11** instead of **8**, in 97% yield.

$^1$H-NMR (DMSO-$d_6$) $\delta$: 0.66 (3H, d, *J*=6.8 Hz), 0.91 (3H, d, *J*=6.8 Hz), 1.58—1.90 (5H, m), 2.18—2.27 (1H, m), 2.54—2.62 (1H, m), 2.76—2.91 (2H, m), 2.99—3.06 (2H, m), 3.15—3.32 (3H, m), 3.40—3.55 (3H, m), 7.06—7.18 (4H, m), 7.23—7.38 (5H, m), 7.74 (1H, t, *J*=5.4 Hz), 10.22 (1H, br s). MS (FAB) *m/z*: 397 ($M^+$+1). *Anal.* Calcd for $C_{25}H_{33}N_2OF \cdot HCl \cdot H_2O$: C, 66.58; H, 8.05; N, 6.21; Cl, 7.86; F, 4.21. Found: C, 66.33; H, 8.05; N, 6.27; Cl, 7.91; F, 4.23.

**2-[2-(2-Methoxyethoxy)phenyl]ethyl 4-Methylbenzenesulfonate (14)** To a mixture of **13** (1.0 g, 7.24 mmol) and $K_2CO_3$ (2.0 g, 14.5 mmol) in DMF (10 mL) was added 2-methoxyethyl bromide (1.1 mL, 11.6 mmol) and the mixture was stirred at 80°C for 30 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=2/3) to give 2-[2-(2-methoxyethoxy)phenyl]-ethanol (1.24 g, 87%) as a colorless oil. To an ice-cooled solution of the alcohol obtained above (1.24 g, 6.32 mmol) in Py (10 mL) was added TsCl (1.6 g, 8.39 mmol) and the mixture was stirred at room temperature for 5 h. The reaction mixture was poured on to ice-water, and extracted with 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 the title compound **14** (1.92 g, 87%) as a yellow oil.

$^1$H-NMR ($CDCl_3$) $\delta$: 2.43 (3H, s), 2.98 (2H, t, *J*=6.8 Hz), 3.41 (3H, s), 3.68 (2H, t, *J*=4.9 Hz), 4.02 (2H, t, *J*=4.9 Hz), 4.25 (2H, t, *J*=6.8 Hz), 6.76 (1H, d, *J*=8.0 Hz), 6.85 (1H, dd, *J*=7.2, 7.2 Hz), 7.07 (1H, dd, *J*=1.6, 7.2 Hz), 7.18 (1H, ddd, *J*=1.6, 7.2, 8.0 Hz), 7.26 (2H, d, *J*=8.8 Hz), 7.68 (2H, d, *J*=8.8 Hz). MS (FAB) *m/z*: 351 ($M^+$+1).

**1-Allyl-3-fluoro-2-(2-methoxyethoxy)benzene (16a)** To a mixture of **15a** (1.0 g, 8.92 mmol) and $K_2CO_3$ (2.0 g, 14.5 mmol) in acetone (15 mL) was added allyl bromide (1.0 mL, 11.7 mmol) and the mixture was stirred at 50°C for 20 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* to give allyl 2-fluorophenyl ether (1.35 g, 99%) as a yellow oil. A mixture of the allyl ether obtained above (1.35 g, 8.87 mmol) in *o*-dichlorobenzene (10 mL) was stirred at 200°C for 12 h. After cooled to room temperature, the reaction mixture was purified by column chromatography on silica gel (AcOEt/hexane=1/15) to give 2-allyl-6-fluorophenol (1.0 g, 74%) as a yellow oil. To a mixture of the phenol obtained above (1.0 g, 6.57 mmol) and $K_2CO_3$ (2.0 g, 14.5 mmol) in DMF (10 mL) was added 2-methoxyethyl bromide (0.90 mL, 9.52 mmol) and the mixture was stirred at 80°C for 8 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=1/20) to give the title compound **16a** (1.02 g, 74%) as a colorless oil.

$^1$H-NMR ($CDCl_3$) $\delta$: 3.44 (3H, s), 3.44—3.48 (2H, m), 3.70 (2H, t, *J*=4.9 Hz), 4.19 (2H, t, *J*=4.9 Hz), 5.03—5.10 (2H, m), 5.91—6.02 (1H, m), 6.90—6.97 (2H, m), 7.26 (1H, br s). MS (EI) *m/z*: 210 ($M^+$).

**1-Allyl-5-fluoro-2-(2-methoxyethoxy)benzene (16b)** The title compound was prepared in the same manner as described for **16a** using **15b** instead of **15a**, in 73% yield.

$^1$H-NMR ($CDCl_3$) $\delta$: 3.34 (2H, br d, *J*=6.8 Hz), 3.45 (3H, s), 3.74 (2H, t, *J*=4.8 Hz), 4.08 (2H, t, *J*=4.8 Hz), 5.05—5.12 (2H, m), 5.90—6.00 (1H, m), 6.78 (1H, dd, *J*=4.8, 8.8 Hz), 6.81—6.90 (2H, m). MS (EI) *m/z*: 210 ($M^+$).

**2-[3-Fluoro-2-(2-methoxyethoxy)phenyl]ethyl 4-Methylbenzenesulfonate (17a)** To a solution of **16a** (1.0 g, 4.76 mmol) in $CHCl_3$ (10 mL) and EtOH (10 mL) was introduced $O_3$ gas at −78°C until **16a** was disappeared on TLC. After the reaction mixture was purged with nitrogen gas, to this reaction mixture was added $NaBH_4$ (1.5 g 39.6 mmol) at −78°C and the mixture was gradually warmed to room temperature for 15 h. The reaction mixture was poured onto HCl*aq.*, and 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=1/2) to give 2-[3-fluoro-

2-(2-methoxyethoxy)phenyl]ethanol (0.99 g, 97%) as a colorless oil. To an ice-cooled solution of the alcohol obtained above (0.99 g, 4.62 mmol) in Py (10 mL) was added TsCl (1.2 g, 6.29 mmol) and the mixture was stirred at room temperature for 2 h. The reaction mixture was poured onto ice-water, and extracted with 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 the title compound **17a** (1.48 g, 87%) as a colorless oil.

$^1$H-NMR ($CDCl_3$) $\delta$: 2.43 (3H, s), 3.02 (2H, t, $J$=6.8 Hz), 3.38 (3H, s), 3.59—3.63 (2H, m), 4.11—4.15 (2H, m), 4.23 (2H, t, $J$=6.8 Hz), 6.85—6.98 (4H, m), 7.25—7.28 (1H, m), 7.67 (2H, d, $J$=8.4 Hz). MS (FAB) *m/z*: 369 ($M^+$+1).

**2-[5-Fluoro-2-(2-methoxyethoxy)phenyl]ethyl 4-Methylbenzenesulfonate (17b)** The title compound was prepared in the same manner as described for **17a** using **16b** instead of **16a**, in 74% yield.

$^1$H-NMR ($CDCl_3$) $\delta$: 2.43 (3H, s), 2.95 (2H, t, $J$=6.8 Hz), 3.41 (3H, s), 3.65—3.69 (2H, m), 3.97—4.01 (2H, m), 4.25 (2H, t, $J$=6.8 Hz), 6.66—6.92 (3H, m), 7.27 (2H, d, $J$=8.0 Hz), 7.68 (2H, d, $J$=8.0 Hz). MS (FAB) *m/z*: 369 ($M^+$+1).

**4-Fluoro-2-(2-methoxyethoxy)benzaldehyde (19)** To a solution of **18** (2.0 g, 12.8 mmol) in MeOH (20 mL) was added sulfuric acid (0.60 mL, 11.3 mmol) and the mixture was stirred at 80°C for 30 h. The reaction mixture was concentrated *in vacuo* and the resulting residue was partitioned between saturated aqueous sodium bicarbonate solution and AcOEt. The organic layer was washed with brine, dried over $Na_2SO_4$ and evaporated *in vacuo* to give methyl 4-fluoro-2-hydroxybenzoate (1.98 g, 91%) as a colorless solid. To a mixture of the phenol obtained above (1.98 g, 11.6 mmol) and $K_2CO_3$ (2.5 g, 18.1 mmol) in DMF (20 mL) was added 2-methoxyethyl bromide (1.5 mL, 15.9 mmol) and the mixture was stirred at 50°C for 30 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=1/3) to give methyl 4-fluoro-2-(2-methoxyethoxy)benzoate (2.48 g, 94%) as a colorless oil. To a mixture of $LiAlH_4$ (0.40 g, 10.5 mmol) in THF (20 mL) was added a solution of the benzoate obtained above (2.48 g, 10.9 mmol) in THF (10 mL) at −40°C and the mixture was gradually warmed to −20°C for 1 h. The reaction was quenched with $Na_2SO_4 \cdot 10H_2O$ (5.0 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 (AcOEt/hexane=1/1) to give [4-fluoro-2-(2-methoxyethoxy)phenyl]methanol (2.14 g, 98%) as a colorless oil. To a mixture of the alcohol obtained above (1.84 g, 9.19 mmol) in $CHCl_3$ (30 mL) was added $MnO_2$ (20.0 g, 230 mmol) and the mixture was stirred at 50°C for 30 h. The insoluble material was removed by filtration and the filtrate was concentrated *in vacuo*. The resulting residue was purified by column chromatography on silica gel (AcOEt/Hexane=1/4) to give the title compound **19** (1.76 g, 97%) as a yellow oil.

$^1$H-NMR ($CDCl_3$) $\delta$: 3.46 (3H, s), 3.81 (2H, t, $J$=4.8 Hz), 4.22 (2H, t, $J$=4.8 Hz), 6.68—6.77 (2H, m), 7.87 (1H, dd, $J$=6.8, 8.4 Hz), 10.42 (1H, s). MS (EI) *m/z*: 198 ($M^+$).

**2-[4-Fluoro-2-(2-methoxyethoxy)phenyl]ethyl 4-Methylbenzenesulfonate (20)** To an ice-cooled mixture of (methoxymethyl)triphenylphosphonium chloride (7.0 g, 20.4 mmol) in THF (50 mL) was added *t*BuOK (2.2 g, 19.6 mmol) and the mixture was stirred at 0°C for 15 min. To this ice-cooled mixture was added **19** (2.04 g, 10.3 mmol) and the mixture was stirred at 0°C for 15 min. 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 ($CHCl_3$/hexane=1/4) to give 4-fluoro-2-(2-methoxyethoxy)-1-(2-methoxyvinyl)benzene (2.06 g, 88%) as a yellow oil. To the methyl ether obtained above (2.06 g, 9.10 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 [4-fluoro-2-(2-methoxyethoxy)phenyl]acetaldehyde (1.95 g, quantitative) as a yellow oil. To an ice-cooled solution of the aldehyde obtained above (1.95 g, 9.19 mmol) in EtOH (15 mL) was added $NaBH_4$ (0.35 g, 9.25 mmol) and the mixture was stirred at room temperature for 2 h. The reaction mixture was poured onto HClaq., and 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=1/1) to give 2-[4-fluoro-2-(2-methoxyethoxy)phenyl]ethanol (1.21 g, 61%) as a colorless oil. To an ice-cooled solution of the alcohol obtained above (1.21 g, 5.64 mmol) in Py (10 mL) was added TsCl (1.5 g, 7.87 mmol) and the mixture was stirred at room temperature for 3 h. The reaction mixture was poured onto ice-water, and extracted with 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 the title compound **20** (1.91 g, 92%) as a colorless oil.

$^1$H-NMR ($CDCl_3$) $\delta$: 2.43 (3H, s), 2.92 (2H, t, $J$=6.8 Hz), 3.41 (3H, s), 3.66—3.70 (2H, m), 3.95—3.99 (2H, m), 4.22 (2H, t, $J$=6.8 Hz), 6.47 (1H, dd, $J$=2.0, 10.8 Hz), 6.54 (1H, ddd, $J$=2.0, 8.4, 8.4 Hz), 6.99 (1H, dd, $J$=6.8, 8.4 Hz), 7.26 (2H, d, $J$=8.4 Hz), 7.66 (2H, d, $J$=8.4 Hz). MS (FAB) *m/z*: 369 ($M^+$+1).

**6-Fluoro-2-(2-methoxyethoxy)benzaldehyde (21)** To a mixture of **15c** (2.0 g, 17.8 mmol) and $K_2CO_3$ (5.0 g, 36.2 mmol) in DMF (10 mL) was added 2-methoxyethyl bromide (2.5 mL, 26.4 mmol) and the mixture was stirred at 60°C for 24 h. The reaction mixture was concentrated *in vacuo* and the resulting residue was partitioned between $H_2O$ and 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=1/10) to give 1-fluoro-3-(2-methoxyethoxy)benzene (2.92 g, 96%) as a colorless oil. To a solution of the fluorobenzene derivative obtained above (2.92 g, 17.2 mmol) in THF (30 mL) was added BuLi (1.60 M in hexane; 14 mL, 22.4 mmol) at −78°C and the mixture was stirred at −78°C for 1.5 h. To the reaction mixture was added DMF (2.0 mL, 25.8 mmol) at −78°C and the mixture was gradually warmed to −10°C for 1 h. The reaction mixture was poured onto HCl*aq*., and 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=1/1) to give the title compound **21** (2.63 g, 77%) as a yellow oil.

$^1$H-NMR ($CDCl_3$) $\delta$: 3.46 (3H, s), 3.80 (2H, t, $J$=4.8 Hz), 4.24 (2H, t, $J$=4.8 Hz), 6.74 (1H, dd, $J$=8.4, 10.4 Hz), 6.78 (1H, d, $J$=8.4 Hz), 7.47 (1H, ddd, $J$=5.6, 8.4, 8.4 Hz), 10.48 (1H, s). MS (EI) $m/z$: 198 ($M^+$).

**2-[6-Fluoro-2-(2-methoxyethoxy)phenyl]ethyl 4-Methylbenzenesulfonate (22)** The title compound was prepared in the same manner as described for **20** using **21** instead of **19**, in 46% yield.

$^1$H-NMR ($CDCl_3$) $\delta$: 2.43 (3H, s), 3.02 (2H, t, $J$=7.2 Hz), 3.42 (3H, s), 3.69—3.72 (2H, m), 4.03—4.07 (2H, m), 4.20 (2H, t, $J$=7.2 Hz), 6.56—6.66 (2H, m), 7.08—7.15 (1H, m), 7.26 (2H, d, $J$=8.0 Hz), 7.71 (2H, d, $J$=8.0 Hz). MS (FAB) $m/z$: 369 ($M^+$+1).

**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 $\mu$g/mL), geneticin (600 $\mu$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 a density of 25000 cells/well. Hank's 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 $\mu$L/well) containing 4 $\mu$M fluo-3 a.m., 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 $\mu$L assay buffer per well. The plates were left to stand at room temperature for 10 min before starting the assay, and the plates were then placed into a FLIPR$^{TM}$ apparatus (Molecular Devices, Berkshire, U.K.) to monitor cell fluorescence. Test compounds (50 $\mu$L each) were added to each well, and the decrease in intercellular calcium concentrations, as measured by the area under the curve (*AUC*) was detected for up to 5 min after the addition of test compounds. The maximum decrease in concentration, expressed as 100% inhibition, was achieved with mibefradil at 3+ $\mu$M. The $IC_{50}$ value was calculated using a nonlinear regression method, using the maximum reaction value as 100%.

**L-Type $Ca^{2+}$ Channel Blocking Activity Study** A7r5 cells (ATCC), a rat aortic cell line endogenously expressing L-type calcium channels, were maintained in D-MEM supplemented with 10% (v/v) fetal bovine serum, penicillin (100 U/mL), streptomycin (100 $\mu$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 a density of 15000 cells/well. The growth medium was removed and replaced with HBSS containing 4 $\mu$M fluo-3 a.m. and 0.04% Pluronic acid F-127 (100 $\mu$L/well) as the dye loading buffer. After a 1.5-h incubation in dye loading buffer, the cells were washed four times with assay buffer, PSS composed of 3 mM KCl, 140 mM NaCl, 1 mM $MgCl_2$, 2 mM $CaCl_2$, 5 mM glucose and 10 mM HEPES. After washing, 100 $\mu$L assay buffer was left in each well. Test compounds (25-$\mu$L) were then added to each well 10 min prior to the addition of 125-$\mu$L high-$K^+$ PSS, which was prepared by replacing NaCl with equimolar KCl. Cell fluorescence was monitored using FLIPR$^{TM}$ (Molecular Devices, U.K.) and the inhibitory effecst of test compounds on the increase in intracellular calcium concentrations by KCl-induced depolarization was evaluated.

**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, and 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 the bath solution being changed every 20 min before drug administration. The amplitude of constriction was measured isometrically using a force-displacement transducer (Nihon Kohden SB-1T) to obtain the spontaneous beat rate by measurement 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 concentration-response curve. The $EC_{30}$ value, which represents the concentration of the compound producing a 30% reduction of the 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 then implanted into the common carotid artery with the opposite end of the catheter 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).

**$Ca^{2+}$ Channel Blocking Activity Study Using a Whole-Cell Patch Clamp Technique** Current recordings were performed at room temperature with standard whole-cell patch clamp techniques using an Axopatch 200B amplifier, Digidata 1200 analog-to-digital converter, and pClamp 6.0 software (Axon Instruments). T-type currents were recorded from HEK293 cells stably expressing the Cav3.1b isoform. The cells were plated on glass coverslips coated with poly-L-lysine and used 1 to 3 d after plating. L-type currents were obtained from rat ventricular myocytes enzymatically isolated from male Wistar rats. For T-type calcium current recordings, the bath solution contained 140 mM NaCl, 2 mM $CaCl_2$, 10 mM glucose and 10 mM HEPES (pH 7.4), and the pipette solution consisted of 110 mM cesium methanesulfonate, 20 mM CsCl, 5 mM Mg-ATP, 11 mM ethylene glycol bis(2-aminoethylether)-*N*,*N*,*N*′,*N*′-tetraacetic acid (EGTA) and 10 mM HEPES (pH 7.2). For

L-type calcium current recordings, the bath solution contained 137 mM TEACl, 5.4 mM CsCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$, 10 mM glucose and 10 mM HEPES (pH 7.4), and the pipette solution consisted of 110 mM cesium methanesulfonate, 20 mM TEACl, 14 mM EGTA, 5 mM MGATP, 5 mM di-Tris creatine phosphate, 0.2 mM Tris-GTP and 10 mM HEPES (pH 7.3). T- and L-type calcium currents were evoked by 200 ms voltage steps from a holding potential of −80 mV to test potentials of −40 mV and 0 mV, respectively.

**Acknowledgements** We thank Dr. Fukushi Hirayama for his helpful support in preparing this manuscript. We are also grateful to Dr. Hironori Harada, Dr. Masakazu Imamura, and Mr. Kyoichi Maeno for their useful advice. Finally, we wish to thank Mr. Kazuhiko Mizukami, Miss Yuriko Komiya, Dr. Noriyasu Kanie, Mr. Satoshi Konagai, and Mr. Eisaku Yamamoto for performing the biological experiments, and the members of the Division of Analytical Science Laboratories for elemental analysis and spectral measurements.

## References and Notes

1) Brini M., Carafoli E., *Cell. Mol. Life Sci.*, **57**, 354—370 (2000).
2) Catterall W. A., Perez-Reyes E., Snutch T. P., Striessnig J., *Pharmacol. Rev.*, **57**, 411—425 (2005).
3) Yamakage M., Namiki A., *Can. J. Anesth.*, **49**, 151—164 (2002).
4) Abernethy D. R., Schwartz J. B., *N. Engl. J. Med.*, **341**, 1447—1457 (1999).
5) Perez-Reyes E., *Physiol. Rev.*, **83**, 117—161 (2003).
6) Mehrke G., Zong X. G., Flockerzi V., Hofmann F., *J. Pharmacol. Exp. Ther.*, **271**, 1483—1488 (1994).
7) Bezprozvanny I., Tsien R. W., *Mol. Pharmacol.*, **48**, 540—549 (1995).
8) Ernst M. E., Kelly M. W., *Pharmacotherapy*, **18**, 463—485 (1998).
9) Kumar P. P., Stotz S. C., Paramashivappa R., Beedle A. M., Zamponi G. W., Rao A. S., *Mol. Pharmacol.*, **61**, 649—658 (2002).
10) 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).
11) 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).
12) 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).
13) 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).
14) 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).
15) 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).
16) Rhim H., Lee Y. S., Park S. J., Chung B. Y., Lee J. Y., *Bioorg. Med. Chem. Lett.*, **15**, 283—286 (2005).
17) 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).
18) Park S. J., Park S. J., Lee M. J., Rhim H., Kim Y., Lee J.-H., Chung B. Y., Lee J. Y., *Bioorg. Med. Chem.*, **14**, 3502—3511 (2006).
19) 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).
20) 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).
21) 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).
22) 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).
23) 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).
24) 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).
25) 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).
26) 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).
27) 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).
28) 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).
29) 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).
30) 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).
31) 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).
32) 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).
33) 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).
34) Smith E. M., Sorota S., Kim H. M., McKittrick B. A., Nechuta T. L., Bennett C., Knutson C., Burnett D. A., Kieselgof 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).
35) 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).
36) 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).
37) Fritch P. C., Krajewski J., *Bioorg. Med. Chem. Lett.*, **20**, 6375—6378 (2010).
38) 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).
39) 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).
40) Giordanetto F., Knerr L., Selmi N., Llinàs A., Lindqvist A., Wang Q.-D., Ståhlberg P., Thorstensson F., Ullah V., Nilsson K., O'Mahony G., Högberg G., Lindhardt E., Strand A., Duker G., *Bioorg. Med. Chem. Lett.*, **21**, 5557—5561 (2011).
41) Woo H. M., Lee Y. S., Roh E. J., Seo S. H., Song C. M., Chung H. J., Pae A. N., Shin K. J., *Bioorg. Med. Chem. Lett.*, **21**, 5910—5915 (2011).
42) Watanuki S., Matsuura K., Tomura Y., Okada M., Okazaki T., Ohta M., Tsukamoto S., *Chem. Pharm. Bull.*, **59**, 1029—1037 (2011).
43) Watanuki S., Matsuura K., Tomura Y., Okada M., Okazaki T., Ohta M., Tsukamoto S., *Bioorg. Med. Chem.*, **19**, 5628—5638 (2011).
44) Watanuki S., Matsuura K., Tomura Y., Okada M., Okazaki T., Ohta M., Tsukamoto S., *Chem. Pharm. Bull.*, **59**, 1376—1385 (2011).
45) During the preparation of this manuscript, the research group of Giordanetto reported that T-type $Ca^{2+}$ channel ($\alpha$1H) inhibitor showed antihypertensive effect in rats after iv infusion. See ref. 40.