Synthesis and Pharmacological Evaluation of 1-Isopropyl-1,2,3,4-tetrahydroisoquinoline Derivatives as Novel Antihypertensive Agents

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A series of 1-isopropyl-1,2,3,4-tetrahydroisoquinoline derivatives were synthesized and their bradycardic activities were evaluated in isolated guinea pig right atria. Structure–activity relationship studies revealed that the introduction of an appropriate substituent and its position on the 1,2,3,4-tetrahydroisoquinoline ring are essential for potent *in vitro* activity. Furthermore, the tether between the piperidyl moiety and the terminal aromatic ring is important for potent antihypertensive activity. Oral administration of 6-fluoro-1-isopropyl-2-{[1-(2-phenylethyl)piperidin-4-yl]carbonyl}-1,2,3,4-tetrahydroisoquinoline (3b) to spontaneously hypertensive rats (SHR) elicited antihypertensive effects without inducing reflex tachycardia, which is often caused by traditional L-type Ca^{2+} channel blockers.

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

Hypertension is the most common cardiovascular disease that increases the risk for endothelial dysfunction, metabolic syndrome, renal dysfunction, congestive heart failure, coronary artery disease and stroke. However, the National Health and Nutrition Examination Survey revealed that approximately 50% of patients with hypertension could not reach their target blood pressure level with the currently available therapies.[1)] In general, treatment of hypertension is carried out with a combination of several classes of antihypertensive drugs that include diuretics, angiotensin—converting enzyme inhibitors, angiotensin II receptor blockers, Ca^{2+} channel blockers and β-blockers. Of these, Ca^{2+} channel blockers are widely used because of their potent hypotensive effects. Ca^{2+} channel blockers inhibit the L-type Ca^{2+} channel, which induces relaxation of vascular smooth muscles.[2)] However, because of their potent hypotensive effects, L-type Ca^{2+} channel blockers can lead to potentially serious problems such as reflex tachycardia, negative inotropy, vasoconstrictive hormone release and peripheral edema.

As an alternative to the traditional L-type Ca^{2+} channel blockers, the T-type Ca^{2+} channel blocker mibefradil (**1**) has been proven to be useful for the treatment of hypertension and angina.[3)] The T-type Ca^{2+} channel is believed to participate in cardiac pace-making,[4)] regulation of vascular tone and hormone secretion.[5,6)] In clinical studies, mibefradil did not cause reflex tachycardia or negative inotropy, and was not associated with reflex activation of neurohormonal and sympathetic systems. Although mibefradil was withdrawn from the market because of significant drug metabolism interactions that were independent of Ca^{2+} channel blockade,[7,8)] its beneficial therapeutic effects are still a driving force for the development of a new generation of T-type Ca^{2+} channel blockers.[9—39)]

Mibefradil is a novel tetraline derivative with two consecutive chiral stereogenic centers. Since the construction of successive chiral centers was a formidable task, we designed compound **2** in which one of the two stereogenic centers of mibefradil was replaced with a nitrogen atom (Fig. 1). Compound **2** showed equipotent bradycardic activity to mibefradil, but it still had a potent inhibitory activity against P450 enzymes.[40)] Further modification of compound **2** aimed at circumventing the P450 enzyme inhibition yielded a piperidine derivative **3a** with potent bradycardic activity.

In this paper, we describe the synthesis, structure–activity relationship, and pharmacological properties of 1-isopropyl-2-{[(1-phenylethyl)piperidin-4-yl]carbonyl}-1,2,3,4-tetrahydroisoquinoline derivatives as novel antihypertensive agents.

Synthesis The preparation of 2-acyl-1-isopropyl-1,2,3,4-tetrahydroisoquinoline derivatives is outlined in Chart 1. Amidation of commercially available phenethylamines (**4a**—**g**) with isobutyryl chloride gave amides **5a**—**g**. The Bischler–Napieralski reaction followed by reduction of imine with sodium borohydride[41)] furnished 1,2,3,4-tetrahydroisoquinolines **6a**—**g**. Condensation of **6a**—**g** with 1-*tert*-butoxycarbonyl(Boc)piperidine-4-carboxylic acid in the presence of 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (WSCD) and 1-hydroxybenzotriazole (HOBt), followed by deprotection of the Boc group by treatment with hydrogen chloride, afforded key intermediates **7a**—**g**. Alkylation of piperidines (**7a**—**g**) was performed using three general methods, Methods A, B and C, summarized in Chart 2.

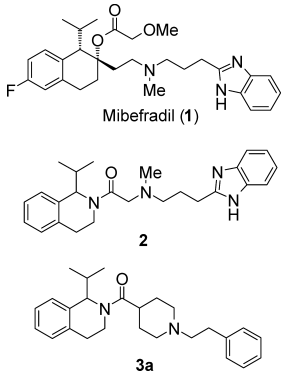

Fig. 1. Chemical Structures of T-Type Ca^{2+} Channel Blocker

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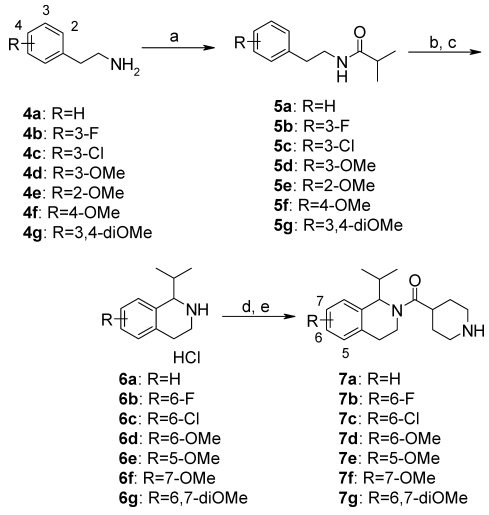
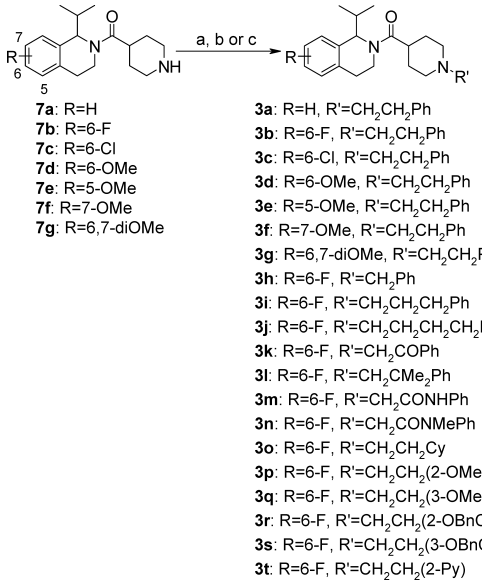


Reagents and conditions: (a) $Me_2CHCOCl$, Py; (b) P_2O_5, $POCl_3$, xylene, reflux; (c) $NaBH_4$, EtOH then HCl; (d) 1-(Boc)piperidine-4-carboxylic acid, WSCD, HOBt, Et_3N, DMF; (e) HCl, AcOEt.

Chart 1



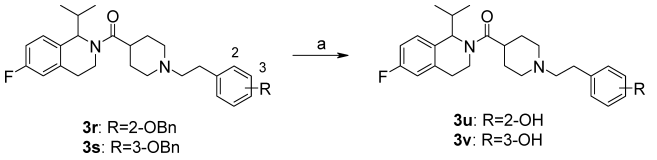
Reagents and conditions: (a) aldehyde, $NaBH(OAc)_3$, AcOH, CH_2Cl_2; (b) alkyl–X (X=Cl, Br, OTs), K_2CO_3, CH_3CN; (c) 2-vinylpyridine, AcOH, MeOH.

Chart 2

Compounds (**3a**—**i**, **3l**, **3p**) were synthesized by reductive alkylation of key intermediates (**7a**—**g**) with the corresponding aldehydes (Method A). Compounds (**3j**—**k**, **3m**—**o**, **3q**—**s**) were prepared by alkylation of **7b** with alkylating agents (Method B). Compound **3t** was obtained by alkylation of **7b** with 2-vinylpyridine in the presence of acetic acid (Method C).

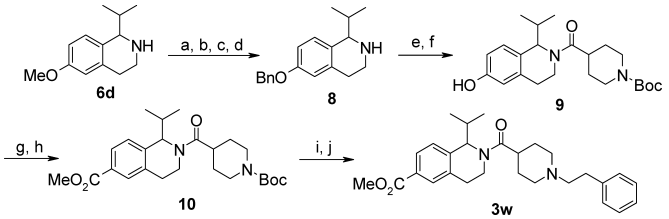
Compounds with a phenol substituent on the phenethyl moiety were synthesized as shown in Chart 3. The benzyl-protected derivatives **3r** and **3s** were obtained using the procedure shown in Chart 2. Hydrogenation of the benzyl group afforded the target compounds (**3u**, **3v**).

Chart 4 shows the synthesis of **3w**. Methyl ether (**6d**) was converted to benzyl ether (**8**) in a four-step sequence. Condensation of **8** with 1-(Boc)piperidine-4-carboxylic acid fol-



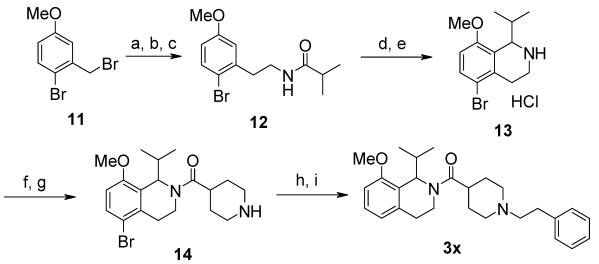
Reagents and conditions: (a) H_2, Pd/C, EtOH.

Chart 3



Reagents and conditions: (a) TFAA, Et_3N, CH_2Cl_2; (b) BBr_3, CH_2Cl_2; (c) BnBr, NaH, DMF; (d) K_2CO_3, MeOH, H_2O; (e) 1-(Boc)piperidine-4-carboxylic acid, WSCD, HOBt, DMF; (f) H_2, Pd/C, EtOH; (g) Tf_2O, 2,6-lutidine, CH_2Cl_2; (h) cat $Pd(OAc)_2$, dppp, Et_3N, MeOH, DMF, CO atmosphere; (i) HCl, AcOEt; (j) $PhCH_2CHO$, $NaBH(OAc)_3$, AcONa, CH_2Cl_2.

Chart 4



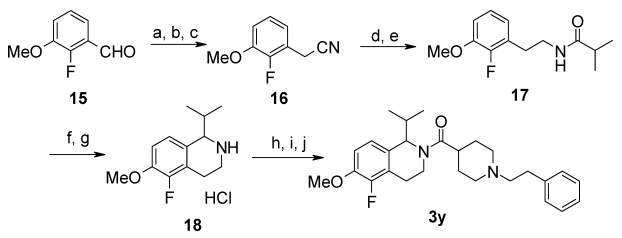
Reagents and conditions: (a) NaCN, EtOH, H_2O; (b) BH_3, THF; (c) $Me_2CHCOCl$, Py; (d) P_2O_5, $POCl_3$, xylene, reflux; (e) $NaBH_4$, EtOH then HCl; (f) 1-(Boc)piperidine-4-carboxylic acid, WSCD, HOBt, Et_3N, DMF; (g) HCl, AcOEt; (h) $PhCH_2CHO$, $NaBH(OAc)_3$, AcOH, CH_2Cl_2; (i) BuLi, THF then AcOH.

Chart 5

lowed by hydrogenolysis gave phenol derivative **9**. Conversion of the hydroxyl group of **9** to a methoxycarbonyl group was accomplished by palladium—catalyzed carbonylation and yielded ester **10**. Deprotection followed by alkylation gave the target compound (**3w**).

Compound **3x** was synthesized as illustrated in Chart 5. To selectively obtain the 8-methoxy derivative **3x**, bromine was used to block the more accessible *para* position. Commercially available benzyl bromide **11** was transformed to amide **12** by substitution with cyanide, reduction with BH_3, and acylation with isobutyryl chloride. The Bischler–Napieralski reaction followed by reduction of imine furnished 1,2,3,4-tetrahydroisoqinoline **13**. Condensation of **13** with 1-(Boc)piperidine-4-carboxylic acid followed by deprotection provided **14**. Alkylation with phenylacetaldehyde followed by removal of the bromide by treatment with butyl lithium gave the desired compound (**3x**).

The 5-fluoro-6-methoxy derivative **3y** was prepared from commercially available aldehyde **15** (Chart 6). Compound **15** was converted into the phenylacetonitrile **16** in a three-step sequence involving reduction with sodium borohydride, bromination of alcohol with triphenylphosphine and carbon tetrabromide, and displacement of the bromide with cyanide. Hydrogenation of the nitrile in the presence of Raney–Ni followed by amidation gave amide **17**. This amide was then



Reagents and conditions: (a) $NaBH_4$, EtOH; (b) CBr_4, PPh_3, CH_2Cl_2; (c) NaCN, EtOH, H_2O; (d) H_2, Raney—Ni, NH_4OH, EtOH; (e) $Me_2CHCOCl$, Py; (f) P_2O_5, $POCl_3$, xylene, reflux; (g) $NaBH_4$, EtOH then HCl; (h) 1-(Boc)piperidine-4-carboxylic acid, WSCD, HOBt, Et_3N, DMF; (i) HCl, AcOEt; (j) $PhCH_2CHO$, $NaBH(OAc)_3$, AcOH, CH_2Cl_2.

Chart 6

converted to **3y** using the methods shown in Charts 1 and 2.

Results and Discussion

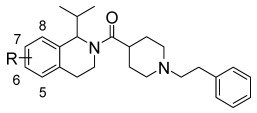
The bradycardic activities of the synthesized compounds designed to inhibit cardiac T-type Ca^{2+} channels were assessed by measuring the effects of these compounds on spontaneous beating rates in the right atria of guinea pig. The EC_{30} values, defined as the concentration of the compounds that elicited a 30% reduction in the spontaneous beating rate from the initial value, were determined by linear regression. Compounds with potent *in vitro* activities were then evaluated *in vivo* by examining their effect on mean blood pressure (MBP) following intravenous administration in anesthetized rats.

We found that the parent compound **3a** exhibited potent bradycardic activity that was comparable with mibefradil (Table 1). Encouraged by this result, we examined the effects of substitutions on the tetrahydroisoquinoline ring of **3a** (Table 1). The introduction of fluorine at position 6 (**3b**) increased the bradycardic activity by about 3-fold relative to **3a** with an EC_{30} value of 0.79 μM. Compounds bearing other substituents, such as Cl- (**3c**), MeO_2C- (**3w**), MeO- (**3d**), were less potent than the 6-F derivative (**3b**). Next, we investigated the position of substituents on the tetrahydroisoquinoline ring of **3a**. Considering synthetic efficiency, methoxy groups were introduced to the tetrahydroisoquinoline ring of **3a**. The 6-methoxy analog **3d** had the most potent activity *in vitro*, while the 8-methoxy analog **3x** had the least potent activity. Compounds bearing additional substituents on the tetrahydroisoquinoline ring (**3y**, **3g**) were less potent than **3d**. These results indicated that the introduction of an appropriate substituent at position 6 of the tetrahydroisoquinoline ring of **3a** is important to confer potent *in vitro* activity.

We next evaluated compounds with various tethers linking the piperidyl moiety and the terminal aromatic ring of **3b** (Table 2). The methylene (**3h**) and propylene analogs (**3i**) had *in vitro* activities comparable to that of **3b**, while the butylene analog (**3j**) was less potent than **3b**. The introduction of carbonyl (**3k**), dimethyl (**3l**) or amide (**3m**, **3n**) groups also reduced activity compared with **3b**. These experiments revealed that linear carbon-chained tethers, particularly one- to three-carbon linkers, elicited potent *in vitro* activity.

Compounds with potent *in vitro* activity were examined in terms of their effect on MBP in anesthetized rats. Table 3 shows the ED_{30} values of the compounds, which represents the required dose to elicit a 30% decrease in MBP compared with that before administration.

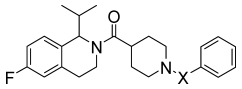
Table 1. Bradycardic Activities of 1-Isopropyl-2-{[1-(2-phenylethyl)-piperidin-4-yl]carbonyl}-1,2,3,4-tetrahydroisoquinoline Derivatives (**3a**—**g**, **3w**—**y**)



Compound	R	EC_{30} (μM)[a]
3a	H	2.1
3b	6-F	0.79
3c	6-Cl	3.2
3w	6-CO_2Me	3.0
3d	6-OMe	1.4
3e	5-OMe	1.7
3f	7-OMe	2.0
3x	8-OMe	4.6
3g	6,7-diOMe	5.7
3y	5-F-6-OMe	1.8
Mibefradil (**1**)	—	2.9

a) Concentration required to elicit a 30% reduction in spontaneous beat rates from baseline in isolated guinea pig right atria. Values are means of at least two experiments.

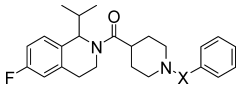
Table 2. Bradycardic Activities of 2-[(1-Alkylpiperidin-4-yl)carbonyl]-1-isopropyl-1,2,3,4-tetrahydroisoquinoline Derivatives (**3b**, **3h**—**n**)



Compound	X	EC_{30} (μM)[a]
3b	CH_2CH_2	0.79
3h	CH_2	0.59
3i	$CH_2CH_2CH_2$	0.95
3j	$CH_2CH_2CH_2CH_2$	1.6
3k	CH_2CO	3.5
3l	CH_2CMe_2	1.9
3m	CH_2CONH	6.0
3n	CH_2CONMe	5.1

a) Concentration required to elicit a 30% reduction in spontaneous beat rates from baseline in isolated guinea pig right atria. Values are means of at least two experiments.

Table 3. Antihypertensive Effects of Selected Compounds in Anesthetized Rats

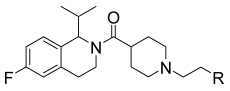


Compound	X	ED_{30} (mg/kg)[a]
3b	CH_2CH_2	0.63
3h	CH_2	2.2
3i	$CH_2CH_2CH_2$	0.49
Mibefradil (**1**)	—	0.46

a) Dose required to elicit a 30% decrease in MBP from baseline in anesthetized rats. Values are means of at least two experiments.

Compound **3b** reduced MBP with an ED_{30} value of 0.63 mg/kg intravenously (i.v.), and its vasodilating effect was similar to that of mibefradil (ED_{30}=0.46 mg/kg i.v.). On the other hand, compound **3h**, whose *in vitro* activity was 5-fold more potent than mibefradil, had a smaller effect on MBP than mibefradil (ED_{30}=2.2 mg/kg i.v.). Compound **3i** showed the most potent *in vivo* activity (ED_{30}=0.49 mg/kg

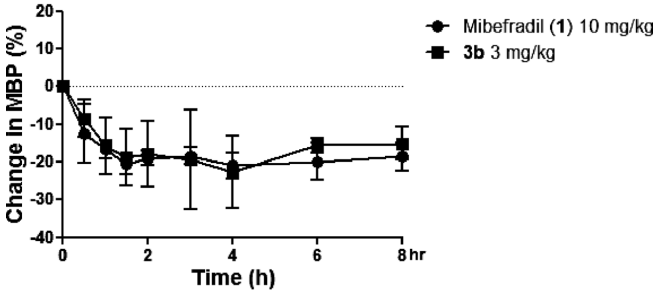
Table 4. Bradycardic Activities of 2-[(1-Alkylpiperidin-4-yl)carbonyl]-1-isopropyl-1,2,3,4-tetrahydroisoquinoline Derivatives (**3b**, **3o**—**q**, **3t**—**v**)



Compound	R	EC_{30} (μM)[a]
3b	Ph	0.79
3o	Cy	2.3
3p	2-$OMeC_6H_4$	2.1
3q	3-$OMeC_6H_4$	2.1
3u	2-OHC_6H_4	1.9
3v	3-OHC_6H_4	3.2
3t	2-Py	2.3

a) Concentration required to elicit a 30% reduction in spontaneous beat rates from baseline in isolated guinea pig right atria. Values are means of at least two experiments.

Graph A



Graph B

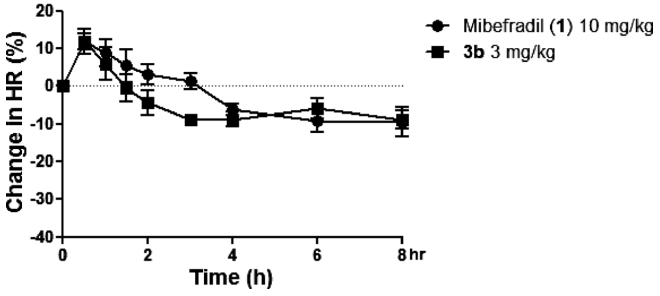


Fig. 2. Effects of **3b** and Mibefradil (**1**) on Mean Blood Pressure (MBP; Graph A) and Heart Rate (HR; Graph B) in Conscious Spontaneously Hypertensive Rats

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

i.v.), despite its moderate *in vitro* activity. These results indicate that the tether between the piperidyl moiety and the terminal benzene ring has a significant impact on the hypotensive effect in anesthetized rats. Although it is unclear whether this hypotensive effect was derived from blockade of the T-type Ca^{2+} channel, we chose compound **3b** as the most suitable compound for further optimization.

Finally, we modified the pendant benzene ring of **3b** (Table 4). Replacement of the benzene ring with a cyclohexane ring decreased the activity 3-fold. To investigate the effects of substituents, MeO and OH groups were introduced to the benzene ring. Both 2- and 3-MeO derivatives (**3p**, **3q**) showed a 3-fold decrease in *in vitro* activity relative to **3b**. Because the 2-OH derivative (**3u**) was more potent than the 3-OH derivative (**3v**), we introduced hydrophilic groups to position 2 of the benzene ring. A pyridine derivative (**3t**) containing a basic nitrogen atom at a similar position to that in mibefradil was less potent than **3b**. Although the introduction of different substituents or the replacement of the benzene ring with another heteroaromatic rings were performed, the compounds bearing an unsubstituted phenethyl group were most potent.

On the basis of the potent bradycardic activity displayed in the isolated guinea pig right atria and the hypotensive effect in anesthetized rats, compound **3b** underwent further pharmacological studies. Mibefradil and **3b** were orally administered to spontaneously hypertensive rats and the effects on MBP and heart rate (HR) were examined. Compound **3b** (3 mg/kg *per os* (*p.o.*)) significantly reduced in MBP, which was sustained for more than 8 h (Fig. 2, Graph A). In this experiment, reflex tachycardia was not observed despite the potent hypotensive activity (Fig. 2, Graph B). Notably, the magnitude and duration of blood pressure lowering induced by **3b** were 3-fold more potent than those induced by mibefradil.

Conclusion

A series of 2-[(1-alkylpiperidin-4-yl)carbonyl]-1-isopropyl-1,2,3,4-tetrahydroisoquinoline derivatives were synthesized and evaluated. Structure–activity relationship studies of this novel class of compounds revealed that the introduction of appropriate substituents and the position of these substituents on the tetrahydroisoquinoline ring are crucial to confer bradycardic effects. Furthermore, the tether linking the piperidyl moiety and the terminal aromatic ring significantly affected the antihypertensive activity of these compounds. Of this series of compounds, 6-fluoro-1-isopropyl-2-{[1-(2-phenylethyl)piperidin-4-yl]carbonyl}-1,2,3,4-tetrahydroisoquinoline (**3b**) showed a potent antihypertensive effect in spontaneously hypertensive rats following oral administration. Further research to obtain novel antihypertensive agents with superior properties to currently available agents is underway and will be described in forthcoming publications.

Experimental

^{1}H-NMR spectra were obtained on a JEOL JNM-EX400 spectrometer and the chemical shifts are expressed in δ (ppm) values with tetramethylsilane as an internal standard. Abbreviations of ^{1}H-NMR signal patterns are as follows: s, singlet; d, doublet; dd, double doublet; dt, double triplet; t, triplet; 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*-{2-[(3-Fluorophenyl)ethyl]}-2-methylpropanamide (5b)** To an ice-cooled solution of 3-fluorophenethylamine (**4b**, 3.0 g, 21.6 mmol) in pyridine (10 ml) was added dropwise isobutyryl chloride (2.4 ml, 22.7 mmol) and the mixture was stirred at room temperature for 16 h. The mixture was poured onto ice-water and the resulting precipitate was collected by filtration to give the title compound **5b** (3.56 g, 79%) as a colorless solid. ^{1}H-NMR ($CDCl_3$) δ: 1.12 (6H, d, J=6.8 Hz), 2.29 (1H, septet, J=6.8 Hz), 2.82 (2H, t, J=6.8 Hz), 3.51 (2H, dt, J=6.8, 6.8 Hz), 5.45 (1H, br s), 6.87—7.00 (3H, m), 7.23—7.30 (1H, m). MS (FAB) m/z: 210 (M^++1).

6-Fluoro-1-isopropyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (6b) To a suspension of **5b** (3.55 g, 17.0 mmol) and P_2O_5 (6.0 g, 42.3 mmol) in xylene (30 ml) was added oxyphosphoryl chloride (15 ml, 161 mmol) and the mixture was refluxed for 2 h. After the mixture was cooled to room temperature, the solution was removed by decantation and the resulting residue was washed with toluene. The resulting residue was quenched with H_2O and 20% aqueous NaOH solution, and then extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo* to give 6-fluoro-1-isopropyl-3,4-dihydroisoquinoline (3.25 g) as a dark drown oil, which was used for the next step without further purification. To an ice-cooled solution of crude 6-fluoro-1-isopropyl-

3,4-dihydroisoquinoline (3.25 g) in EtOH (30 ml) was added potionwise sodium borohydride (1.5 g, 39.7 mmol) and the mixture was stirred at room temperature for 2 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 converted to its hydrochloride salt by treating it with 4 M HCl–AcOEt (4.5 ml, 18.0 mmol). The crude salt was suspended with AcOEt and filtered to give the title compound **6b** (3.22 g, 82%) as a colorless powder. ^{1}H-NMR (DMSO-d_6) δ: 0.85 (3H, d, J=6.8 Hz), 1.09 (3H, d, J=6.8 Hz), 2.42—2.51 (1H, m), 2.91—3.00 (1H, m), 3.01—3.24 (2H, m), 3.34—3.45 (1H, m), 4.53 (1H, br s), 7.10—7.15 (2H, m), 7.33—7.38 (1H, m), 8.90 (1H, br s), 10.00 (1H, br s). MS (FAB) m/z: 194 (M^++1).

4-[(6-Fluoro-1-isopropyl-1,2,3,4-tetrahydroisoquinolin-2-yl)carbonyl]-piperidine (7b) To an ice-cooled suspension of **6b** (0.50 g, 2.18 mmol), 1-(Boc)piperidine-4-carboxylic acid (0.57 g, 2.49 mmol), HOBt (0.35 g, 2.59 mmol), and Et_3N (1.0 ml, 7.17 mmol) in *N*,*N*-dimethylformamide (DMF) (10 ml) was added WSCD (0.50 g, 2.61 mmol) and the mixture was stirred at room temperature for 5 d. The reaction mixture was concentrated *in vacuo* and partitioned between H_2O and AcOEt. The organic layer was washed successively with 5% aqueous citric acid solution, saturated aqueous sodium bicarbonate solution, and brine, dried over Na_2SO_4, and evaporated *in vacuo*. The resulting residue was purified by column chromatography on silica gel (AcOEt/hexane=1/2) to give *tert*-butyl 4-[(6-fluoro-1-isopropyl-1,2,3,4-tetrahydroisoquinolin-2-yl)carbonyl]piperidine-1-carboxylate (0.89 g, quantitative) as a light yellow oil. To an ice-cooled solution of the *N*-Boc derivative obtained above (0.89 g, 2.20 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 24 h. The reaction mixture was concentrated *in vacuo* and the 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*. The resulting residue was purified by column chromatography on silica gel (MeOH/$CHCl_3$=10/90) to give the title compound **7b** (0.69 g, qunatitative) as a light orange oil. ^{1}H-NMR ($CDCl_3$) δ: 0.92—1.01 (6H, m), 1.40—2.05 (5H, m), 2.59—3.84 (9H, m), 4.36 and 5.31 (1H, d, J=8.7 Hz), 6.82—6.88 (2H, m), 7.07—7.13 (1H, m). MS (electrospray ionization (ESI)) m/z: 305 (M^++1).

6-Fluoro-1-isopropyl-2-{[1-(2-phenylethyl)piperidin-4-yl]carbonyl}-1,2,3,4-tetrahydroisoquinoline Hydrochloride (3b). (Method A) To an ice-cooled solution of **7b** (0.40 g, 1.31 mmol), phenylacetaldehyde (0.20 ml, 1.80 mmol), and acetic acid (0.50 ml) in CH_2Cl_2 (10 ml) was added sodium triacetoxyborohydride (0.40 g, 1.89 mmol) and the mixture was stirred at room temperature for 15 h. The reaction mixture was concentrated *in vacuo* and partitioned between saturated aqueous sodium bicarbonate solution and $CHCl_3$. 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 6-fluoro-1-isopropyl-2-{[1-(2-phenylethyl)-piperidin-4-yl]carbonyl}-1,2,3,4-tetrahydroisoquinoline (0.53 g) as a colorless solid. The compound was converted to its hydrochloride salt by treating it with 4 M HCl–AcOEt (0.40 ml, 2.00 mmol). The crude salt was suspended with Et_2O and filtered to give the title compound **3b** (0.47 g, 81%) as a colorless powder. ^{1}H-NMR (DMSO-d_6) δ: 0.84—0.95 (6H, m), 1.52—2.18 (5H, m), 2.81—4.23 (13H, m), 4.64 and 5.17 (1H, d, J=9.2 Hz), 6.96—7.06 (3H, m), 7.20—7.37 (5H, m), 10.54 and 10.80 (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, 67.37; H, 7.72; N, 5.85; Cl, 7.63; F, 4.08.

4-[(1-Isopropyl-1,2,3,4-tetrahydroisoquinolin-2-yl)carbonyl]piperidine (7a) The title compound was prepared in the same manner as described for **7b** using **6a**[41] instead of **6b**, in 98% yield. ^{1}H-NMR ($CDCl_3$) δ: 0.93—1.02 (6H, m), 1.39—2.07 (5H, m), 2.59—3.81 (9H, m), 4.38 and 5.33 (1H, d, J=9.2 Hz), 7.08—7.26 (4H, m). MS (FAB) m/z: 287 (M^++1).

1-Isopropyl-2-{[1-(2-phenylethyl)piperidin-4-yl]carbonyl}-1,2,3,4-tetrahydroisoquinoline Hydrochloride (3a) The title compound was prepared in the same manner as described for **3b** using **7a** instead of **7b**, in 82% yield. ^{1}H-NMR (DMSO-d_6) δ: 0.85—0.96 (6H, m), 1.50—2.18 (5H, m), 2.75—4.25 (13H, m), 4.60 and 5.16 (1H, d, J=9.2 Hz), 7.15—7.37 (9H, m), 10.03 and 10.06 (1H, br s). MS (FAB) m/z: 391 (M^++1). *Anal.* Calcd for $C_{26}H_{34}N_2O\cdot HCl\cdot H_2O$: C, 70.17; H, 8.38; N, 6.29; Cl, 7.97. Found: C, 70.09; H, 8.36; N, 6.13; Cl, 8.01.

***N*-{2-[(3-Chlorophenyl)ethyl]}-2-methylpropanamide (5c)** The title compound was prepared in the same manner as described for **5b** using **4c** instead of **4b**, in 92% yield. ^{1}H-NMR ($CDCl_3$) δ: 1.12 (6H, d, J=6.8 Hz), 2.29 (1H, septet, J=6.8 Hz), 2.80 (2H, t, J=6.8 Hz), 3.49 (2H, dt, J=6.8, 6.8 Hz), 5.46 (1H, br s), 7.05—7.09 (1H, m), 7.16—7.26 (3H, m). MS (FAB) m/z: 226 (M^++1).

6-Chloro-1-isopropyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (6c) The title compound was prepared in the same manner as described for **6b** using **5c** instead of **5b**, in 57% yield. ^{1}H-NMR (DMSO-d_6) δ: 0.84 (3H, d, J=6.8 Hz), 1.08 (3H, d, J=6.8 Hz), 2.41—2.50 (1H, m), 2.88—3.00 (1H, m), 3.00—3.24 (2H, m), 3.40—3.45 (1H, m), 4.43 (1H, br s), 7.23—7.36 (3H, m), 8.77 (1H, br s), 9.88 (1H, br s). MS (FAB) m/z: 210 (M^++1).

4-[(6-Chloro-1-isopropyl-1,2,3,4-tetrahydroisoquinolin-2-yl)carbonyl]-piperidine (7c) The title compound was prepared in the same manner as described for **7b** using **6c** instead of **6b**. This compound was directly used for the next step.

6-Chloro-1-isopropyl-2-{[1-(2-phenylethyl)piperidin-4-yl]carbonyl}-1,2,3,4-tetrahydroisoquinoline Hydrochloride (3c) The title compound was prepared in the same manner as described for **3b** using **7c** instead of **6b**, in 70% yield (3 steps). ^{1}H-NMR (DMSO-d_6) δ: 0.84—0.95 (6H, m), 1.51—2.17 (5H, m), 2.60—4.24 (13H, m), 4.64 and 5.17 (1H, d, J=9.2 Hz), 7.17—7.37 (8H, m), 10.48 and 10.75 (1H, br s). MS (FAB) m/z: 425 (M^++1). *Anal.* Calcd for $C_{26}H_{33}N_2OCl\cdot HCl\cdot H_2O$: C, 65.13; H, 7.57; N, 5.84; Cl, 14.79. Found: C, 65.36; H, 7.55; N, 5.65; Cl, 14.41.

***N*-{2-[(3-Methoxyphenyl)ethyl]}-2-methylpropanamide (5d)** To an ice-cooled solution of 3-methoxyphenethylamine (**4d**, 3.0 g, 21.6 mmol) in pyridine (10 ml) was added dropwise isobutyryl chloride (2.2 ml, 20.9 mmol) and the mixture was stirred at room temperature for 16 h. The mixture was poured onto ice-water and then extracted with AcOEt. The organic layer was washed successively with 1 M $HCl_{aq.}$, saturated aqueous sodium bicarbonate solution, and brine, dried over Na_2SO_4, and evaporated *in vacuo* to give the title compound **5d** (4.33 g, 99%) as a colorless solid. ^{1}H-NMR ($CDCl_3$) δ: 1.12 (6H, d, J=6.8 Hz), 2.28 (1H, septet, J=6.8 Hz), 2.79 (2H, t, J=6.8 Hz), 3.51 (2H, dt, J=6.8, 6.8 Hz), 3.80 (3H, s), 5.45 (1H, br s), 6.73—6.81 (3H, m), 7.22 (1H, dd, J=7.6, 7.6 Hz). MS (FAB) m/z: 222 (M^++1).

1-Isopropyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (6d) The title compound was prepared in the same manner as described for **6b** using **5d** instead of **5b**, in 88% yield. ^{1}H-NMR (DMSO-d_6) δ: 0.84 (3H, d, J=6.8 Hz), 1.07 (3H, d, J=6.8 Hz), 2.37—2.48 (1H, m), 2.84—2.95 (1H, m), 3.00—3.20 (2H, m), 3.38—3.45 (1H, m), 3.75 (3H, s), 4.34 (1H, d, J=4.8 Hz), 6.80 (1H, d, J=2.4 Hz), 6.85 (1H, dd, J=2.4, 5.3 Hz), 7.20 (1H, d, J=5.3 Hz). MS (FAB) m/z: 206 (M^++1).

4-[(1-Isopropyl-6-methoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)carbonyl]piperidine (7d) The title compound was prepared in the same manner as described for **7b** using **6d** instead of **6b**, in quantitative yield. ^{1}H-NMR ($CDCl_3$) δ: 0.90—1.03 (6H, m), 1.40—2.09 (5H, m), 2.59—3.85 (12H, m), 4.33 and 5.26 (1H, d, J=9.2 Hz), 6.64—6.74 (2H, m), 6.99 and 7.06 (1H, d, J=8.4 Hz). MS (FAB) m/z: 317 (M^++1).

1-Isopropyl-6-methoxy-2-{[1-(2-phenylethyl)piperidin-4-yl]carbonyl}-1,2,3,4-tetrahydroisoquinoline Oxalate (3d) The title compound was prepared in the same manner as described for **3b** using **7d** instead of **7b**, in 80% yield. ^{1}H-NMR (DMSO-d_6) δ: 0.82—0.94 (6H, m), 1.48—2.10 (5H, m), 2.70—4.25 (16H, m), 4.52 and 5.09 (1H, d, J=9.2 Hz), 6.70—6.78 (2H, m), 7.07 and 7.12 (1H, d, J=8.4 Hz), 7.21—7.37 (5H, m). MS (FAB) m/z: 421 (M^++1). *Anal.* Calcd for $C_{27}H_{36}N_2O_2\cdot C_2H_2O_4\cdot H_2O$: C, 65.89; H, 7.63; N, 5.30. Found: C, 65.68; H, 7.68; N, 5.62.

***N*-{2-[(2-Methoxyphenyl)ethyl]}-2-methylpropanamide (5e)** The title compound was prepared in the same manner as described for **5b** using **4e** instead of **4b**, in 79% yield. ^{1}H-NMR ($CDCl_3$) δ: 1.11 (6H, d, J=6.8 Hz), 2.27 (1H, septet, J=6.8 Hz), 2.84 (2H, t, J=6.8 Hz), 3.48 (2H, dt, J=6.8, 6.8 Hz), 3.84 (3H, s), 5.66 (1H, br s), 6.85—6.93 (2H, m), 7.12 (1H, d, J=5.7 Hz), 7.22 (1H, dd, J=5.7, 7.6 Hz). MS (FAB) m/z: 222 (M^++1).

1-Isopropyl-5-methoxy-1,2,3,4-tetrahydroisoquinoline (6e) The title compound was prepared in the same manner as described for **6b** using **5e** instead of **5b**, in 18% yield. ^{1}H-NMR ($CDCl_3$) δ: 0.79 (3H, d, J=6.8 Hz), 1.10 (3H, d, J=6.8 Hz), 2.32—2.40 (1H, m), 2.63—2.70 (1H, m), 2.75—2.82 (1H, m), 2.90—3.00 (1H, m), 3.35—3.45 (1H, m), 3.82 (3H, s), 4.02 (1H, br s), 6.74 (1H, d, J=7.6 Hz), 6.79 (1H, d, J=7.6 Hz), 7.14 (1H, dd, J=7.6, 7.6 Hz). MS (FAB) m/z: 206 (M^++1).

4-[(1-Isopropyl-5-methoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)carbonyl]piperidine (7e) The title compound was prepared in the same manner as described for **3b** using **6e** instead of **6b**. This compound was directly used for the next step.

1-Isopropyl-5-methoxy-2-{[1-(2-phenylethyl)piperidin-4-yl]carbonyl}-1,2,3,4-tetrahydroisoquinoline Oxalate (3e) The title compound was prepared in the same manner as described for **3b** using **7e** instead of **7b**, in 62% yield (3 steps). ^{1}H-NMR (DMSO-d_6) δ: 0.82—0.97 (6H, m), 1.48—2.10 (5H, m), 2.70—4.25 (16H, m), 4.53 and 5.14 (1H, d, J=9.6 Hz), 6.75—6.86 (2H, m), 7.11—7.17 (1H, m), 7.22—7.37 (5H, m). MS (FAB) m/z: 421

($M^+ + 1$). *Anal.* Calcd for $C_{27}H_{36}N_2O_2 \cdot C_2H_2O_4 \cdot 0.5H_2O$: C, 67.03; H, 7.56; N, 5.39. Found: C, 67.25; H, 7.74; N, 5.37.

***N*-{2-[(4-Methoxyphenyl)ethyl]}-2-methylpropanamide (5f)** The title compound was prepared in the same manner as described for **5d** using **4f** instead of **4d**, in 93% yield. ^{1}H-NMR ($CDCl_3$) δ: 1.11 (6H, d, J=6.8 Hz), 2.27 (1H, septet, J=6.8 Hz), 2.75 (2H, t, J=6.8 Hz), 3.48 (2H, dt, J=6.8, 6.8 Hz), 3.80 (3H, s), 5.41 (1H, br s), 6.85 (2H, d, J=6.4 Hz), 7.10 (2H, d, J=6.4 Hz). MS (FAB) *m/z*: 222 ($M^+ + 1$).

1-Isopropyl-7-methoxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (6f) The title compound was prepared in the same manner as described for **6b** using **5f** instead of **5b**, in 30% yield. ^{1}H-NMR (DMSO-d_6) δ: 0.83 (3H, d, J=6.8 Hz), 1.07 (3H, d, J=6.8 Hz), 2.37—2.52 (1H, m), 2.84—2.95 (1H, m), 3.00—3.20 (2H, m), 3.38—3.50 (1H, m), 3.73 (3H, s), 4.30—4.34 (1H, m), 6.78—6.89 (2H, m), 7.12—7.22 (1H, m), 8.55 (1H, br s), 9.75 (1H, br s). MS (FAB) *m/z*: 206 ($M^+ + 1$).

4-[(1-Isopropyl-7-methoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)carbonyl]piperidine (7f) The title compound was prepared in the same manner as described for **7b** using **6f** instead of **6b**, in 100% yield. ^{1}H-NMR ($CDCl_3$) δ: 0.90—1.05 (6H, m), 1.40—2.12 (5H, m), 2.60—3.85 (12H, m), 4.33 and 5.29 (1H, d, J=9.2 Hz), 6.60—6.78 (2H, m), 6.99—7.10 (1H, m). MS (FAB) *m/z*: 317 ($M^+ + 1$).

1-Isopropyl-7-methoxy-2-{[1-(2-phenylethyl)piperidin-4-yl]carbonyl}-1,2,3,4-tetrahydroisoquinoline Oxalate (3f) The title compound was prepared in the same manner as described for **3b** using **7f** instead of **7b**, in 79% yield. ^{1}H-NMR (DMSO-d_6) δ: 0.82—0.97 (6H, m), 1.48—2.08 (5H, m), 2.72—4.26 (16H, m), 4.57 and 5.15 (1H, d, J=9.2 Hz), 6.71—6.83 (2H, m), 7.05—7.15 (1H, m), 7.21—7.36 (5H, m). MS (FAB) *m/z*: 421 ($M^+ + 1$).

***N*-{2-[(3,4-Dimethoxyphenyl)ethyl]}-2-methylpropanamide (5g)** The title compound was prepared in the same manner as described for **5d** using **4g** instead of **4d**, in 73% yield. ^{1}H-NMR ($CDCl_3$) δ: 1.11 (6H, d, J=6.8 Hz), 2.28 (1H, septet, J=6.8 Hz), 2.76 (2H, t, J=6.8 Hz), 3.49 (2H, dt, J=6.8, 6.8 Hz), 3.87 (6H, br s), 5.43 (1H, br s), 6.70—6.75 (2H, m), 6.81 (1H, d, J=8.8 Hz). MS (FAB) *m/z*: 252 ($M^+ + 1$).

6,7-Dimethoxy-1-isopropyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (6g) The title compound was prepared in the same manner as described for **6b** using **5g** instead of **5b**, in 78% yield. ^{1}H-NMR (DMSO-d_6) δ: 0.83 (3H, d, J=6.8 Hz), 1.09 (3H, d, J=6.8 Hz), 2.42—2.55 (1H, m), 2.76—2.88 (1H, m), 2.92—3.04 (1H, m), 3.04—3.14 (1H, m), 3.38—3.44 (1H, m), 3.73 (3H, s), 3.74 (3H, s), 4.33 (1H, d, J=4.0 Hz), 6.79 (1H, s), 6.83 (1H, s). MS (FAB) *m/z*: 236 ($M^+ + 1$).

4-[(6,7-Dimethoxy-1-isopropyl-1,2,3,4-tetrahydroisoquinolin-2-yl)carbonyl]piperidine (7g) The title compound was prepared in the same manner as described for **7b** using **6g** instead of **6b**. This compound was directly used for the next step.

6,7-Dimethoxy-1-isopropyl-2-{[1-(2-phenylethyl)piperidin-4-yl]carbonyl}-1,2,3,4-tetrahydroisoquinoline Oxalate (3g) The title compound was prepared in the same manner as described for **3b** using **7g** instead of **7b**, in 88% yield (3 steps). ^{1}H-NMR (DMSO-d_6) δ: 0.81—1.00 (6H, m), 1.48—2.10 (5H, m), 2.70—4.30 (19H, m), 4.53 and 5.12 (1H, d, J=8.8 Hz), 6.73—6.79 (2H, m), 7.21—7.36 (5H, m). MS (FAB) *m/z*: 451 ($M^+ + 1$). *Anal.* Calcd for $C_{28}H_{38}N_2O_3 \cdot C_2H_2O_4 \cdot H_2O$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.83; H, 7.60; N, 4.88.

6-Fluoro-1-isopropyl-2-[(1-benzylpiperidin-4-yl)carbonyl]-1,2,3,4-tetrahydroisoquinoline Hydrochloride (3h) The title compound was prepared in the same manner as described for **3b** using benzaldehyde instead of phenylacetaldehyde, in 60% yield. ^{1}H-NMR (DMSO-d_6) δ: 0.78—0.90 (6H, m), 1.48—2.22 (5H, m), 2.70—4.32 (11H, m), 4.59 and 5.14 (1H, d, J=8.7 Hz), 6.93—7.06 (2H, m), 7.13—7.28 (1H, m), 7.46 (3H, br s), 7.55—7.66 (2H, m), 10.40—10.90 (1H, m). MS (FAB) *m/z*: 395 ($M^+ + 1$). *Anal.* Calcd for $C_{25}H_{31}N_2OF \cdot HCl \cdot H_2O$: C, 66.87; H, 7.63; N, 6.24; F, 4.23; Cl, 7.90. Found: C, 66.67; H, 7.60; N, 5.90; F, 4.27; Cl, 7.75.

6-Fluoro-1-isopropyl-2-{[1-(3-phenylpropyl)piperidin-4-yl]carbonyl}-1,2,3,4-tetrahydroisoquinoline Oxalate (3i) The title compound was prepared in the same manner as described for **3b** using hydrocinnamaldehyde instead of phenylacetaldehyde, in 68% yield. ^{1}H-NMR (DMSO-d_6) δ: 0.81—0.94 (6H, m), 1.45—2.08 (7H, m), 2.62 (2H, t, J=7.6 Hz), 2.74—4.24 (11H, m), 4.58 and 5.15 (1H, d, J=9.2 Hz), 6.94—7.07 (2H, m), 7.17—7.34 (6H, m). MS (FAB) *m/z*: 423 ($M^+ + 1$). *Anal.* Calcd for $C_{27}H_{35}N_2OF \cdot C_2H_2O_4 \cdot 0.7H_2O$: C, 66.32; H, 7.37; N, 5.33; F, 3.62. Found: C, 66.29; H, 7.33; N, 5.35; F, 3.66.

6-Fluoro-1-isopropyl-2-{[1-(4-phenylbutyl)piperidin-4-yl]carbonyl}-1,2,3,4-tetrahydroisoquinoline Oxalate (3j). (Method B) To a suspension of **7b** (0.35 g, 1.15 mmol) and K_2CO_3 (0.25 g, 1.81 mmol) in CH_3CN (10 ml) was added 4-phenylbutyl bromide (0.33 g, 1.55 mmol) and the mixture was stirred at 70 °C for 15 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 (MeOH/$CHCl_3$=3/97) to give 6-fluoro-1-isopropyl-2-{[1-(4-phenylbutyl)piperidin-4-yl]carbonyl}-1,2,3,4-tetrahydroisoquinoline (0.50 g) as a pale yellow oil. The compound was converted to its oxalate by treating it with oxalic acid (91 mg, 1.01 mmol). The crude salt was suspended with CH_3CN and filtered to give the title compound **3j** (0.45 g, 73%) as a colorless powder. ^{1}H-NMR (DMSO-d_6) δ: 0.81—0.95 (6H, m), 1.46—2.08 (9H, m), 2.61 (2H, t, J=7.2 Hz), 2.74—4.24 (11H, m), 4.59 and 5.15 (1H, d, J=9.0 Hz), 6.94—7.08 (2H, m), 7.15—7.32 (6H, m). MS (FAB) *m/z*: 437 ($M^+ + 1$). *Anal.* Calcd for $C_{28}H_{37}N_2OF \cdot C_2H_2O_4 \cdot 1.2H_2O$: C, 65.72; H, 7.61; N, 5.11; F, 3.47. Found: C, 65.72; H, 7.61; N, 5.11; F, 3.47.

6-Fluoro-1-isopropyl-2-[(1-phenacylpiperidin-4-yl)carbonyl]-1,2,3,4-tetrahydroisoquinoline Oxalate (3k) The title compound was prepared in the same manner as described for **3j** using phenacyl bromide instead of 4-phenylbutyl bromide, in 60% yield. ^{1}H-NMR (DMSO-d_6) δ: 0.80—0.96 (6H, m), 1.45—2.14 (5H, m), 2.64—4.24 (9H, m), 4.57 and 4.62 (2H, s), 4.64 and 5.18 (1H, d, J=9.2 Hz), 6.95—7.07 (2H, m), 7.18—7.30 (1H, m), 7.59 (2H, dd, J=7.6, 8.0 Hz), 7.72 (1H, dd, J=7.6, 8.0 Hz), 7.97—8.04 (2H, m). MS (FAB) *m/z*: 423 ($M^+ + 1$). *Anal.* Calcd for $C_{26}H_{31}N_2O_2F \cdot C_2H_2O_4 \cdot 0.2H_2O$: C, 65.15; H, 6.52; N, 5.43; F, 3.68. Found: C, 65.02; H, 6.45; N, 5.20; F, 3.66.

6-Fluoro-1-isopropyl-2-{[1-(2-methyl-2-phenylpropyl)piperidin-4-yl]carbonyl}-1,2,3,4-tetrahydroisoquinoline Oxalate (3l) The title compound was prepared in the same manner as described for **3b** using 2-methyl-2-phenylpropionaldehyde instead of phenylacetaldehyde, in 26% yield. ^{1}H-NMR (DMSO-d_6) δ: 0.77—0.91 (6H, m), 1.20—2.04 (11H, m), 2.42—4.22 (11H, m), 4.54 and 5.14 (1H, d, J=9.2 Hz), 6.93—7.06 (2H, m), 7.16—7.26 (2H, m), 7.30—7.38 (2H, m), 7.42—7.50 (2H, m). MS (FAB) *m/z*: 436 ($M^+ + 1$). *Anal.* Calcd for $C_{28}H_{37}N_2OF \cdot C_2H_2O_4 \cdot 1.1H_2O$: C, 65.94; H, 7.60; N, 5.13; F, 3.48. Found: C, 65.95; H, 7.61; N, 5.09; F, 3.49.

2-{4-[(6-Fluoro-1-isopropyl-1,2,3,4-dihydroisoquinolin-2-yl)carbonyl]-piperidin-1-yl}-*N*-phenylacetamide Fumarate (3m) The title compound was prepared in the same manner as described for **3j** using *N*-phenylchloroacetamide instead of 4-phenylbutyl bromide, in 72% yield. ^{1}H-NMR (DMSO-d_6) δ: 0.82—0.94 (6H, m), 1.30—2.05 (5H, m), 2.21—2.35 (2H, m), 2.62—4.22 (9H, m), 4.60 and 5.17 (1H, d, J=9.2 Hz), 6.62 (2H, s), 6.94—7.08 (3H, m), 7.21 (1H, dd, J=6.0, 8.4 Hz), 7.26—7.34 (2H, m), 7.59—7.65 (2H, m), 9.71 (1H, s). MS (FAB) *m/z*: 438 ($M^+ + 1$). *Anal.* Calcd for $C_{26}H_{32}N_3O_2F \cdot C_4H_4O_4 \cdot 0.3H_2O$: C, 64.46; H, 6.60; N, 7.52; F, 3.40. Found: C, 64.55; H, 6.54; N, 7.62; F, 3.34.

2-{4-[(6-Fluoro-1-isopropyl-1,2,3,4-dihydroisoquinolin-2-yl)carbonyl]-piperidin-1-yl}-*N*-methyl-*N*-phenylacetamide Fumarate (3n) The title compound was prepared in the same manner as described for **3j** using *N*-methyl-*N*-phenylchloroacetamide instead of 4-phenylbutyl bromide, in 70% yield. ^{1}H-NMR (DMSO-d_6) δ: 0.79—0.91 (6H, m), 1.20—2.24 (7H, m), 2.50—4.25 (12H, m), 4.53 and 5.15 (1H, d, J=9.2 Hz), 6.61 (2H, s), 6.93—7.05 (2H, m), 7.16—7.47 (6H, m). MS (FAB) *m/z*: 452 ($M^+ + 1$). *Anal.* Calcd for $C_{27}H_{34}N_3O_2F \cdot C_4H_4O_4 \cdot 0.7H_2O$: C, 64.17; H, 6.84; N, 7.24; F, 3.27. Found: C, 64.07; H, 6.80; N, 7.17; F, 3.25.

6-Fluoro-1-isopropyl-2-{[(2-cyclohexylethyl)piperidin-4-yl]carbonyl}-1,2,3,4-tetrahydroisoquinoline Oxalate (3o) The title compound was prepared in the same manner as described for **3j** using 2-cyclohexylethyl bromide instead of 4-phenylbutyl bromide, in 50% yield. ^{1}H-NMR (DMSO-d_6) δ: 0.81—0.96 (6H, m), 1.05—1.34 (3H, m), 1.45—2.08 (15H, m), 2.77—4.22 (11H, m), 4.60 and 5.15 (1H, d, J=9.2 Hz), 6.95—7.08 (2H, m), 7.18—7.28 (1H, m). MS (FAB) *m/z*: 415 ($M^+ + 1$). *Anal.* Calcd for $C_{26}H_{39}N_2OF \cdot C_2H_2O_4 \cdot 0.1H_2O$: C, 66.41; H, 8.20; N, 5.53; F, 3.75. Found: C, 66.30; H, 8.18; N, 5.53; F, 3.76.

6-Fluoro-1-isopropyl-2-({1-[2-(2-methoxyphenyl)ethyl]piperidin-4-yl}-carbonyl)-1,2,3,4-tetrahydroisoquinoline Oxalate (3p) The title compound was prepared in the same manner as described for **3b** using 2-methoxyphenylacetaldehyde instead of phenylacetaldehyde, in 38% yield. ^{1}H-NMR (DMSO-d_6) δ: 0.82—0.96 (6H, m), 1.50—2.10 (5H, m), 2.79—4.24 (16H, m), 4.61 and 5.17 (1H, d, J=9.2 Hz), 6.88—6.94 (1H, m), 6.95—7.10 (3H, m), 7.16—7.30 (3H, m). MS (FAB) *m/z*: 439 ($M^+ + 1$). *Anal.* Calcd for $C_{27}H_{35}N_2O_2F \cdot C_2H_2O_4 \cdot 0.2H_2O$: C, 65.45; H, 7.08; N, 5.26; F, 3.57. Found: C, 65.45; H, 7.15; N, 5.27; F, 3.52.

6-Fluoro-1-isopropyl-2-({1-[2-(3-methoxyphenyl)ethyl]piperidin-4-yl}-carbonyl)-1,2,3,4-tetrahydroisoquinoline Oxalate (3q) The title compound was prepared in the same manner as described for **3j** using 2-(3-methoxyphenyl)ethyl *p*-toluenesulfonate instead of 4-phenylbutyl bromide,

in 68% yield. ^{1}H-NMR (DMSO-d_6) δ: 0.82—0.96 (6H, m), 1.50—2.10 (5H, m), 2.79—4.23 (16H, m), 4.60 and 5.17 (1H, d, J=9.2 Hz), 6.79—6.87 (3H, m), 6.95—7.08 (2H, m), 7.18—7.29 (2H, m). MS (FAB) m/z: 439 (M^++1). *Anal.* Calcd for $C_{27}H_{35}N_2O_2F \cdot C_2H_2O_4 \cdot 2H_2O$: C, 61.69; H, 7.32; N, 4.96; F, 3.36. Found: C, 61.68; H, 7.30; N, 4.91; F, 3.35.

2-({1-[2-(2-Benzyloxyphenyl)ethyl]piperidin-4-yl}carbonyl)-6-fluoro-1-isopropyl-1,2,3,4-tetrahydroisoquinoline (3r) The title compound was prepared in the same manner as described for **3j** using 2-(2-benzyloxyphenyl)ethyl *p*-toluenesulfonate instead of 4-phenylbutyl bromide, in 92% yield. ^{1}H-NMR ($CDCl_3$) δ: 0.91—1.01 (6H, m), 1.52—2.18 (5H, m), 2.44—3.84 (13H, m), 4.33 and 5.32 (1H, d, J=8.8 Hz), 5.08 (2H, s), 6.80—7.47 (12H, m). MS (ESI) m/z: 515 (M^++1).

2-({1-[2-(3-Benzyloxyphenyl)ethyl]piperidin-4-yl}carbonyl)-6-fluoro-1-isopropyl-1,2,3,4-tetrahydroisoquinoline (3s) The title compound was prepared in the same manner as described for **3j** using 2-(3-benzyloxyphenyl)ethyl *p*-toluenesulfonate **20**[42] instead of 4-phenylbutyl bromide, in 87% yield. This compound was directly used for the next step.

6-Fluoro-1-isopropyl-2-({1-[2-(2-pyridyl)ethyl]piperidin-4-yl}carbonyl)-1,2,3,4-tetrahydroisoquinoline Oxalate (3t). (Method C) To a solution of **7b** (0.45 g, 1.48 mmol) and AcOH (0.10 ml, 1.75 mmol) in MeOH (5.0 ml) was added 2-vinylpyridine (0.16 g, 1.52 mmol) and the mixture was stirred at 100 °C for 7 h. The reaction mixture was concentrated *in vacuo* and 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*. The resulting residue was purified by column chromatography on silica gel (MeOH/$CHCl_3$=10/90) to give 6-fluoro-1-isopropyl-2-({1-[2-(2-pyridyl)ethyl]piperidin-4-yl}carbonyl)-1,2,3,4-tetrahydroisoquinoline (0.50 g) as a colorless oil. The compound was converted to its oxalate by treating it with oxalic acid (94 mg, 1.04 mmol). The crude salt was suspended with CH_3CN and filtered to give the title compound **3t** (0.42 g, 57%) as a colorless powder. ^{1}H-NMR (DMSO-d_6) δ: 0.81—0.96 (6H, m), 1.52—2.12 (5H, m), 2.74—4.24 (13H, m), 4.62 and 5.17 (1H, d, J=9.2 Hz), 6.95—7.10 (2H, m), 7.17—7.37 (3H, m), 7.73—7.79 (1H, m), 8.49—8.53 (1H, m). MS (FAB) m/z: 410 (M^++1). *Anal.* Calcd for $C_{25}H_{32}N_3OF \cdot C_2H_2O_4 \cdot 1.7H_2O$: C, 61.16; H, 7.11; N, 7.93; F, 3.58. Found: C, 61.05; H, 6.93; N, 7.88; F, 3.61.

6-Fluoro-2-({1-[2-(2-hydroxyphenyl)ethyl]piperidin-4-yl}carbonyl)-1-isopropyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (3u) To a solution of **3r** (0.73 g, 1.42 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 8 h. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The resulting residue was purified by column chromatography on silica gel (AcOEt/$CHCl_3$=1/3) to give 6-fluoro-2-({1-[2-(2-hydroxyphenyl)ethyl]piperidin-4-yl}carbonyl)-1-isopropyl-1,2,3,4-tetrahydroisoquinoline (0.43 g) as a light yellow foam. The compound was converted to its hydrochloride salt by treating it with 4 M HCl–AcOEt (0.50 ml, 2.00 mmol). The crude salt was suspended with AcOEt and filtered to give the title compound **3u** (0.40 g, 62%) as a colorless powder. ^{1}H-NMR (DMSO-d_6) δ: 0.82—0.96 (6H, m), 1.50—2.20 (5H, m), 2.76—4.26 (13H, m), 4.62 and 5.17 (1H, d, J=9.2 Hz), 6.76 (1H, dd, J=7.6, 7.6 Hz), 6.87 (1H, d, J=7.6 Hz), 6.95—7.15 (4H, m), 7.19—7.30 (1H, m), 9.70 (1H, s), 10.12 (1H, s). MS (FAB) m/z: 425 (M^++1). *Anal.* Calcd for $C_{26}H_{33}N_2O_2F \cdot HCl \cdot 0.1H_2O$: C, 67.47; H, 7.45; N, 6.05; Cl, 7.66; F, 4.10. Found: C, 67.45; H, 7.51; N, 5.94; Cl, 7.71; F, 4.10.

6-Fluoro-2-({1-[2-(3-hydroxyphenyl)ethyl]piperidin-4-yl}carbonyl)-1-isopropyl-1,2,3,4-tetrahydroisoquinoline Oxalate (3v) The title compound was prepared in the same manner as described for **3u** using **3s** instead of **3r**, in 42% yield. ^{1}H-NMR (DMSO-d_6) δ: 0.81—0.96 (6H, m), 1.50—2.10 (5H, m), 2.76—4.26 (13H, m), 4.61 and 5.17 (1H, d, J=9.2 Hz), 6.61—6.71 (3H, m), 6.95—7.30 (4H, m). MS (FAB) m/z: 425 (M^++1).

6-Benzyloxy-1-isopropyl-1,2,3,4-tetrahydroisoquinoline (8) To an ice-cooled solution of **6d** (5.0 g, 20.7 mmol) and Et_3N (8.0 ml, 57.4 mmol) in CH_2Cl_2 (50 ml) was added trifluoroacetic anhydride (5.3 g, 25.2 mmol) and the mixture was stirred at room temperature for 7 d. The reaction mixture was concentrated *in vacuo* and partitioned between H_2O and AcOEt. The organic layer was washed successively with 5% aqueous citric acid solution, saturated aqueous sodium bicarbonate solution, and brine, dried over Na_2SO_4, and evaporated *in vacuo*. The resulting residue was purified by column chromatography on silica gel (AcOEt/hexane=1/4) to give 6-methoxy-1-isopropyl-2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline (6.43 g, quantitative) as a light yellow oil. To a solution of the trifluoroacetamide obtained above (6.43 g, 20.7 mmol) in CH_2Cl_2 (30 ml) was added BBr_3 (14 g, 55.9 mmol) at −78 °C and the mixture was gradually warmed to 0 °C for 2 h. The reaction mixture was poured onto ice-water and then extracted with $CHCl_3$. 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 (AcOEt/hexane=1/3) to give 6-hydroxy-1-isopropyl-2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline (6.07 g, quantitative) as a light orange foam. To an ice-cooled mixture of the phenol obtained above (3.0 g, 10.4 mmol), NaH (60% dispersion in mineral oil; 0.50 g, 12.5 mmol) in DMF (20 ml) was added BnBr (2.3 g, 13.4 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 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 6-benzyloxy-1-isopropyl-2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline (3.71 g, 95%) as a light yellow oil. To a solution of the trifluoroacetamide obtained above (3.71 g, 9.83 mmol) and H_2O (10 ml) in MeOH (20 ml) was added K_2CO_3 (3.0 g, 21.7 mmol) and the mixture was stirred at 70 °C for 23 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 **8** (2.83 g, quantitative) as a colorless solid. ^{1}H-NMR ($CDCl_3$) δ: 0.75 (3H, d, J=6.8 Hz), 1.10 (3H, d, J=6.8 Hz), 2.25—2.36 (1H, m), 2.58—2.68 (1H, m), 2.79—2.96 (2H, m), 3.24—3.33 (1H, m), 3.90 (1H, br s), 5.03 (2H, s), 6.71 (1H, d, J=2.8 Hz), 6.80 (1H, dd, J=2.8, 8.4 Hz), 7.06 (1H, d, J=8.4 Hz), 7.28—7.46 (5H, m). MS (FAB) m/z: 282 (M^++1).

***tert*-Butyl 4-[(6-Hydroxy-1-isopropyl-1,2,3,4-tetrahydroisoquinolin-2-yl)carbonyl]piperidine-1-carboxylate (9)** To an ice-cooled suspension of **8** (2.83 g, 9.83 mmol), 1-(Boc)piperidine-4-carboxylic acid (2.4 g, 10.5 mmol), and HOBt (1.4 g, 10.4 mmol) in DMF (30 ml) was added WSCD (2.0 g, 10.4 mmol) and the mixture was stirred at room temperature for 10 d. The reaction mixture was concentrated *in vacuo* and partitioned between H_2O and AcOEt. The organic layer was washed successively with 5% aqueous citric acid solution, saturated aqueous sodium bicarbonate solution, and brine, dried over Na_2SO_4, and evaporated *in vacuo*. The resulting residue was purified by column chromatography on silica gel (AcOEt/hexane=1/1) to give *tert*-butyl 4-[(6-benzyloxy-1-isopropyl-1,2,3,4-tetrahydroisoquinolin-2-yl)carbonyl]piperidine-1-carboxylate (3.46 g, 71%) as a colorless foam. To a solution of the *N*-Boc derivative obtained above (3.46 g, 7.02 mmol) in EtOH (30 ml) was added 10% Pd/C (10 w/w %; 0.50 g), 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 the title compound **9** (2.92 g, quantitative) as a black oil. ^{1}H-NMR ($CDCl_3$) δ: 0.85—1.03 (6H, m), 1.44 and 1.46 (9H, s), 1.53—2.00 (5H, m), 2.60—4.22 (9H, m), 4.29 and 5.23 (1H, d, J=9.2 Hz), 6.60—6.68 (2H, m), 6.92—6.98 (1H, m). MS (FAB) m/z: 403 (M^++1).

***tert*-Butyl 4-[(1-Isopropyl-6-methoxycarbonyl-1,2,3,4-tetrahydroisoquinolin-2-yl)carbonyl]piperidine-1-carboxylate (10)** To a solution of **9** (0.50 g, 1.24 mmol), 2,6-lutidine (0.30 ml, 2.58 mmol), and DMAP (10 mg, 89 μmol) in CH_2Cl_2 (10 ml) was added trifluoromethanesulfonic anhydride (0.30 ml, 1.78 mmol) at −78 °C 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* to give *tert*-butyl 4-{[1-isopropyl-6-{[(trifluoromethyl)sulfonyl]oxy}-1,2,3,4-tetrahydroisoquinolin-2-yl]carbonyl}piperidine-1-carboxylate (0.67 g) as a light yellow oil, which was used for the next step without further purification. To a solution of crude trifluoromethanesulfonate obtained above (0.67 g), Et_3N (0.50 ml, 3.59 mmol), dppp (56 mg, 136 μmol), and MeOH (4.0 ml) in DMF (10 ml) was added $Pd(OAc)_2$ (30 mg, 134 μmol) and the mixture was stirred under CO atmosphere at 70 °C for 15 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=1/1) to give the title compound **10** (0.50 g, 2 steps 91%) as a colorless foam. ^{1}H-NMR ($CDCl_3$) δ: 0.89—1.05 (6H, m), 1.44 and 1.46 (9H, s), 1.50—2.10 (5H, m), 2.62—4.22 (12H, m), 4.42 and 5.40 (1H, d, J=9.2 Hz), 7.16 and 7.22 (1H, d, J=7.6 Hz), 7.80—7.85 (2H, m). MS (FAB) m/z: 445 (M^++1).

1-Isopropyl-6-methoxycarbonyl-2-{[1-(2-phenylethyl)piperidin-4-yl]-carbonyl}-1,2,3,4-tetrahydroisoquinoline Fumarate (3w) To an ice-cooled solution of **10** (0.50 g, 1.12 mmol) in AcOEt (5 ml) was added 4 M HCl–AcOEt (5.0 ml, 20.0 mmol) and the mixture was stirred at room temperature for 14 h. The reaction mixture was concentrated *in vacuo* to give 4-[(1-isopropyl-6-methoxycarbonyl-1,2,3,4-tetrahydroisoquinolin-2-yl)carbonyl]piperidine hydrochloride (0.43 g, qunatitative) as a colorless solid, which was used for the next step without further purification. To an ice-

cooled suspension of crude piperidine derivative obtained above (0.43 g), phenylacetaldehyde (0.20 ml, 1.80 mmol), and sodium acetate (0.40 g, 4.88 mmol) in CH_2Cl_2 (10 ml) was added sodium triacetoxyborohydride (0.40 g, 1.89 mmol) and the mixture was stirred at room temperature for 15 h. The reaction mixture was concentrated *in vacuo* and partitioned between saturated aqueous sodium bicarbonate solution and $CHCl_3$. 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-isopropyl-6-methoxycarbonyl-2-{[1-(2-phenylethyl)piperidin-4-yl]-carbonyl}-1,2,3,4-tetrahydroisoquinoline (0.55 g) as a yellow oil. The compound was converted to its fumarate by treating it with fumaric acid (0.13 g, 1.12 mmol). The crude salt was suspended with acetone and filtered to give the title compound **3w** (0.50 g, 79%) as a colorless powder. ^{1}H-NMR (DMSO-d_6) δ: 0.82—0.96 (6H, m), 1.30—2.38 (7H, m), 2.60—3.23 (9H, m), 3.60—3.72 (1H, m), 3.84 (3H, s), 3.88—3.98 (1H, m), 4.66 and 5.25 (1H, d, J=9.2 Hz), 6.58 (2H, s), 7.15—7.41 (6H, m), 7.72—7.80 (2H, m). MS (FAB) *m/z*: 449 (M^++1). *Anal.* Calcd for $C_{28}H_{36}N_2O_3 \cdot C_4H_4O_4 \cdot 0.4H_2O$: C, 67.21; H, 7.19; N, 4.90. Found: C, 67.25; H, 7.22; N, 4.88.

***N*-{2-[(2-Bromo-5-methoxyphenyl)ethyl]}-2-methylpropanamide (12)** To a solution of **11** (2.0 g, 7.14 mmol) and H_2O (10 ml) in EtOH (20 ml) was added sodium cyanide (0.40 g, 8.16 mmol) and the mixture was stirred at 80 °C 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* to give (2-bromo-5-methoxyphenyl)acetonitrile (2.5 g) as a light orange solid, which was used for the next step without further purification. To a solution of crude nitrile obtained above (2.5 g) in tetrahydrofuran (THF) (20 ml) was added $BH_3 \cdot SMe_2$ (10 M in SMe_2; 3.0 ml, 30.0 mmol), and the mixture was stirred at 80 °C for 20 h. After the reaction mixture was cooled to room temperature, MeOH (30 ml) was added. The reaction mixture was concentrated *in vacuo* and then 4 M HCl–AcOEt (10 ml, 40.0 mmol) was added. The resulting solid was collected by filtration to give 2-bromo-5-methoxyphenethylamine hydrochloride (0.73 g) as a colorless solid. Using this 2-bromo-5-methoxyphenethylamine hydrochloride instead of **4d**, the title compound was prepared in the same manner as described for **5b** in 38% yield (3 steps). ^{1}H-NMR ($CDCl_3$) δ: 1.13 (6H, d, J=6.8 Hz), 2.31 (1H, septet, J=6.8 Hz), 2.94 (2H, t, J=6.8 Hz), 3.54 (2H, dt, J=6.8, 6.8 Hz), 3.77 (3H, s), 5.51 (1H, br s), 6.68 (1H, dd, J=3.2, 8.4 Hz), 6.77 (1H, d, J=3.2 Hz), 7.43 (1H, d, J=8.4 Hz). MS (FAB) *m/z*: 300, 302 (M^++1).

5-Bromo-1-isopropyl-8-methoxy-1,2,3,4-tetrahydroisoquinoline (13) The title compound was prepared in the same manner as described for **6b** using **12** instead of **5b**, in 85% yield. ^{1}H-NMR ($CDCl_3$) δ: 0.83 (3H, d, J=6.8 Hz), 1.00 (3H, d, J=6.8 Hz), 2.28—2.38 (1H, m), 2.60—2.72 (1H, m), 2.82—3.00 (2H, m), 3.30—3.40 (1H, m), 3.78 (3H, s), 4.17—4.22 (1H, m), 6.61 (1H, d, J=8.8 Hz), 7.38 (1H, d, J=8.8 Hz). MS (FAB) *m/z*: 284, 286 (M^++1).

4-[(5-Bromo-1-isopropyl-8-methoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)carbonyl]piperidine (14) The title compound was prepared in the same manner as described for **7b** using **13** instead of **6b**. This compound was directly used for the next step.

1-Isopropyl-8-methoxy-2-{[1-(2-phenylethyl)piperidin-4-yl]carbonyl}-1,2,3,4-tetrahydroisoquinoline Oxalate (3x) 5-Bromo-1-isopropyl-8-methoxy-2-{[1-(2-phenylethyl)piperidin-4-yl]carbonyl}-1,2,3,4-tetrahydroisoquinoline was prepared in the same manner as described for **3b** using **14** instead of **7b** in quantitative yield (2 steps). To a solution of the arylbromide obtained above (0.26 g, 521 μmol) in THF (10 ml) was added BuLi (1.58 M in hexane; 1.0 ml, 1.58 mmol) at −78 °C and the mixture was stirred at −78 °C for 1 h. To the reaction mixture was added AcOH (0.50 ml, 8.73 mmol) at −78 °C and the mixture was stirred at room temperature for 1 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-isopropyl-8-methoxy-2-{[1-(2-phenylethyl)piperidin-4-yl]carbonyl}-1,2,3,4-tetrahydroisoquinoline (0.17 g) as a light yellow oil. The compound was converted to its oxalate by treating it with oxalic acid (36 mg, 400 μmol). The crude salt was suspended with CH_3CN and filtered to give the title compound **3x** (0.15 g, 58%) as a colorless powder. ^{1}H-NMR (DMSO-d_6) δ: 0.75—1.01 (6H, m), 1.30—2.10 (5H, m), 2.80—4.00 (16H, m), 4.90 and 5.65 (1H, d, J=9.6 Hz), 6.77—6.92 (2H, m), 7.14—7.36 (6H, m). MS (FAB) *m/z*: 421 (M^++1). *Anal.* Calcd for $C_{27}H_{36}N_2O_2 \cdot C_2H_2O_4 \cdot 0.7H_2O$: C, 66.57; H, 7.59; N, 5.35. Found: C, 66.69; H, 7.89; N, 5.25.

(2-Fluoro-3-methoxyphenyl)acetonitrile (16) To an ice-cooled solution of 2-fluoro-3-methoxybenzaldehyde (**15**, 1.0 g, 6.49 mmol) in EtOH (10 ml) was added potionwise sodium borohydride (0.15 g, 3.97 mmol) and the mixture was stirred at room temperature for 2 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* to give 2-fluoro-3-methoxybenzylalcohol (1.05 g) as a pale yellow solid. To an ice-cooled solution of the benzylalcohol obtained above (1.05 g, 6.72 mmol) and carbon tetrabromide (2.5 g, 7.54 mmol) in CH_2Cl_2 (10 ml) was added triphenylphosphine (1.9 g, 7.24 mmol) and the mixture was stirred at 0 °C for 30 min. The reaction mixture was concentrated *in vacuo* and 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 (AcOEt/hexane=1/10) to give 2-fluoro-3-methoxybenzyl bromide (1.60 g) as a light yellow oil. To a solution of the benzyl bromide obtained above (1.60 g) and H_2O (5.0 ml) in EtOH (10 ml) was added sodium cyanide (0.37 g, 7.55 mmol) and the mixture was stirred at 70 °C for 16 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=1/8) to give title compound **16** (0.80 g, 3 steps 72%) as a colorless solid. ^{1}H-NMR ($CDCl_3$) δ: 3.77 (2H, s), 3.90 (3H, s), 6.93—7.14 (3H, m). MS (EI) *m/z*: 165 (M^+).

***N*-{2-[(2-Fluoro-3-methoxyphenyl)ethyl]}-2-methylpropanamide (17)** To a suspension of Raney–Ni (*ca.* 1.0 g), 28 w/w% NH_4OH (1.0 ml) in EtOH (10 ml) was added **16** (0.80 g, 4.84 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-(2-fluoro-3-methoxyphenyl)ethylamine (0.85 g, quantitative) as a black oil. Using the phenethylamine obtained above instead of **4d**, the title compound was prepared in the same manner as described for **5d** in 90% yield. ^{1}H-NMR ($CDCl_3$) δ: 1.11 (6H, d, J=6.8 Hz), 2.29 (1H, septet, J=6.8 Hz), 2.87 (2H, t, J=6.8 Hz), 3.51 (2H, dt, J=6.8, 6.8 Hz), 3.88 (3H, s), 6.76 (1H, dd, J=7.2, 8.4 Hz), 6.85 (1H, dd, J=7.2, 8.4 Hz), 7.01 (1H, dd, J=7.2, 8.4 Hz). MS (FAB) *m/z*: 240 (M^++1).

5-Fluoro-1-isopropyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline Hydrochloride (18) The title compound was prepared in the same manner as described for **6b** using **17** instead of **5b**, in 88% yield. ^{1}H-NMR (DMSO-d_6) δ: 0.86 (3H, d, J=6.8 Hz), 1.08 (3H, d, J=6.8 Hz), 2.39—2.50 (1H, m), 2.90—3.00 (1H, m), 3.10—3.50 (3H, m), 3.84 (3H, s), 4.38 (1H, br s), 7.08—7.16 (2H, m), 8.71 (1H, br s), 9.71 (1H, br s). MS (FAB) *m/z*: 224 (M^++1).

5-Fluoro-1-isopropyl-6-methoxy-2-{[1-(2-phenylethyl)piperidin-4-yl]-carbonyl}-1,2,3,4-tetrahydroisoquinoline Fumarate (3y) The title compound was prepared in the same manner as described in Charts 1 and 2, in 73% yield (3 steps). ^{1}H-NMR (DMSO-d_6) δ: 0.78—0.99 (6H, m), 1.30—2.05 (5H, m), 2.25—2.42 (2H, m), 2.62—4.44 (14H, m), 4.55 and 5.14 (1H, d, J=9.2 Hz), 6.58 (2H, s), 6.90—7.04 (2H, m), 7.15—7.35 (5H, m). MS (FAB) *m/z*: 439 (M^++1). *Anal.* Calcd for $C_{27}H_{35}N_2O_2F \cdot C_4H_4O_4$: C, 67.13; H, 7.09; N, 5.05; F, 3.43. Found: C, 66.85; H, 7.24; N, 5.04; F, 3.44.

Pharmacology *in Vitro* Study Male Hartley guinea pigs (250—400 g) were sacrificed by decapitation under isofluran 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 dimethyl sulfoxide (DMSO) and diluted with saline to the desired concentration was added to the bath solution cumulatively at 30-min intervals, and a concentration–response curve was thus constructed. The EC_{30} value for the concentration of the compounds producing a 30% reduction from initial spontaneous beat rate was determined *via* linear regression.

Pharmacology *in Vivo* Study (i.v.) Male Wister rats (250—300 g) were anesthetized with pentobarbital (60 mg/kg intraperitoneally (i.p.)). One polyethylene cannulae (PE-50) was implanted in the left femoral artery and one was implanted in the left femoral vein. Blood pressure was measured with a pressure transducer (Nihon Kohden DX-100) coupled to the cannula introduced into femoral artery and a pressure amplifier (Nihon Kohden AP-621G), and continuously recorded *via* a polygraph system. Mean blood pres-

sure (MBP) was calculated from the following formula; MBP=DBP+(SBP−DBP)/3, where DBP represents diastolic blood pressure and SBP represents systolic blood pressure. Heart rate was measured with a cardiotachometer (Nihon Kohden AT-600G) triggered by the pulsewave of blood pressure. A ED_{30} value that mean the dose of the compounds producing a 30% reduction from initial MBP, was determined by linear regression.

Pharmacology *in Vivo* Study (*p.o.*) Male SHR rats (300—350 g) were anesthetized with pentobarbital (60 mg/kg i.p.), and a polyethylene cannula (PE-50) was implanted in the common carotid artery. The other end of the catheter was then routed to an exit site at the back of the neck. Animals were allowed a 1- to 2-d 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 doses of 3 and 10 mg/kg (the salt form).

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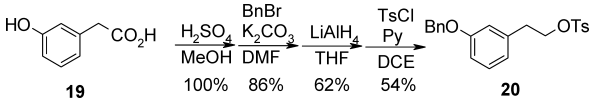
42) 2-(3-Benzyloxy)ethyl *p*-toluenesulfonate **20** was synthesized as following scheme.



20; ^{1}H-NMR (DMSO-d_6) δ: 2.41 (3H, s), 2.92 (2H, t, J=6.8 Hz), 4.21 (2H, t, J=6.8 Hz), 5.01 (2H, s), 6.66—6.75 (2H, m), 6.81—6.84 (1H, m), 7.17 (1H, dd, J=6.4, 7.2 Hz), 7.28 (1H, s), 7.30—7.44 (6H, m), 7.69 (2H, d, J=8.4 Hz). MS (ESI) m/z: 405 (M^++Na).