Synthesis and Pharmacological Evaluation of 2-(3-Piperidyl)-1,2,3,4-tetrahydroisoquinoline Derivatives as Specific Bradycardic Agents

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Novel 1,2,3,4-tetrahydroisoquinoline derivatives bearing directly a cyclic amine at the 2-position were prepared and examined for their bradycardic activities in isolated right atria and in anesthetized rats. The structure–activity relationships (SAR) study revealed that the 2-(3-piperidyl)-1,2,3,4-tetrahydroisoquinoline skeleton is essential for the appearance of potent *in vitro* activity, and that the presence of at least one methoxy group at the 6- or 7-position of the 1,2,3,4-tetrahydroisoquinoline ring is important to exert potent *in vitro* activity. *In vivo* tests of selected compounds demonstrated that 2-(1-benzyl-3-piperidyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (6c) exhibited potent bradycardic activity with negligible influence on mean blood pressure in rats, although its potency is a half of that of Zatebradine.

Key words specific bradycardic agent; 1,2,3,4-tetrahydroisoquinoline; Zatebradine; dimethoxy

Myocardial ischemia, irrespective of its clinical expression, always results from an imbalance between the supply and demand of oxygen. This imbalances may lead to irreversible myocardial damage. As heart rate is a major determinant of myocardial oxygen consumption,[1,2] agents that can reduce sinus heart rate are of great interest for the treatment of ischemic heart desease. Reductions in sinus heart rate can be achieved by administering cardiodepressive agents, such as β-adrenoreceptor antagonists[3] or some calcium channel blockers.[4] However, these agents may cause concomitant negative inotropic and hypotensive effects[5,6] which are potentially deleterious during ischemia.

Recently, the pharmacological properties of a novel class of substances, specific bradycardic agents, have been described.[7] Such agents induce sinus bradycardia at concentrations that are devoid of additional haemodynamic effects.[8—11] Specific bradycardic agents have been shown to act by reducing the heart's demand for oxygen and by increasing the diastolic period which in turn induces increases in the subendocardial blood flow.[12—14] One of the most potent specific bradycardic agent described so far, Zatebradine (7,8-dimethoxy-3-(3-{[2-(3,4-dimethoxyphenyl)ethyl]methylamino} propyl)-1,3,4,5-tetrahydro-2*H*-benzazepin-2-one hydrochloride, UL-FS 49) (**2**), has been reported to reduce heart rate without concomitant negative inotropic or hypotensive effects not only in animal models[10,15] but also in clinical trials.[10] Zatebradine was found by modifying Verapamil (**1**),[16] a prominent calcium channel blocker, by replacing the asymmetric α-isopropylphenylacetonitrile moiety with a benzazepinone ring.[17] This modification brought about a drastic change in the pharmacological profile, especially in terms of blood pressure and cardiac contractility.[16] This result indicates that the benzene-fused hetrocyclic ring is critical for the selectivity for heart rate reduction *versus* the influences on blood pressure and cardiac contractility. The structure–activity relationships (SAR) of Zatebradine also demonstrates that the basic nitrogen atom is essential for bradycardic activity and that the 3,4-dimethoxyphenethyl moiety is tolerable to structural modifications.[17] From these results, we assumed that the spatial orientation between the benzene-fused hetrocyclic ring and the basic nitrogen atom is important to exhibit potent and specific bradycardic activities, and that linear structure is not always necessary.

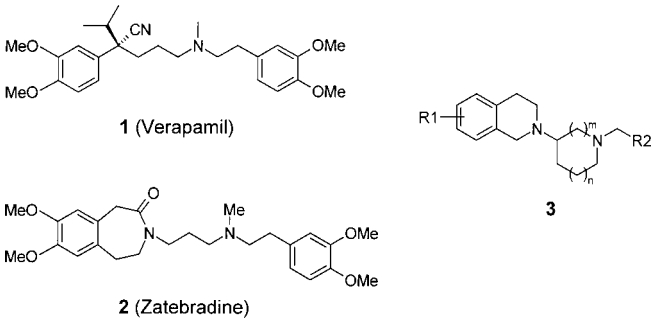

Fig. 1

Our work to find a novel type of specific bradycardic agent was focused on searching for a novel skeleton containing a benzene-fused hetrocyclic ring and a basic nitrogen atom which exert specific bradycardic activities. We designed 1,2,3,4-tetrahydroisoquinoline derivatives **3** bearing directly a cyclic amine at the 2-position, which may possess more rigid structure than that of Zatebradine. In this paper, we describe the synthesis, the SAR and the pharmacological properties of compounds **3**.

Chemistry

The 1,2,3,4-tetrahydroisoquinolines (**4a**—**f**),[18,19] which are either commercially available or known, were condensed with *N*-benzylpiperidones (**5a**, **5c**) or a *N*-benzylpyrrolidone (**5b**) by reductive alkylation in the presence of sodium triacetoxyborohydride ($NaBH(OAc)_3$)[20] and acetic acid to afford compounds **6a**—**h** shown in Chart 1. The key intermediate amine **10** was synthesized *via* the route described in Chart 1. Compound **4a** was subjected to reductive alkylation with a *N*-*tert*-butoxycarbonyl-3-piperidone (**8**),[21] which was obtained by Swern oxidation[22] of *N*-*tert*-butoxycarbonyl-3-

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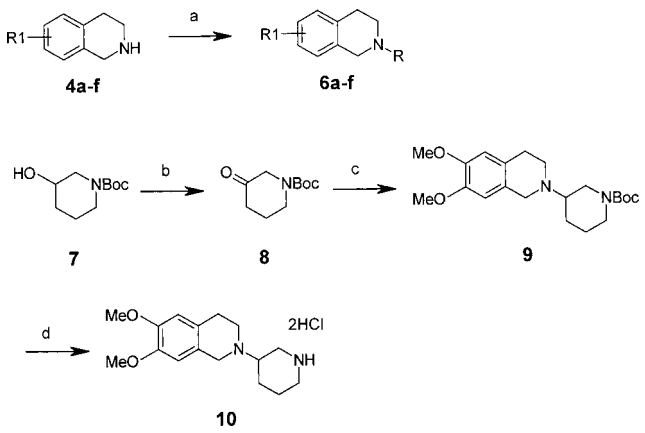
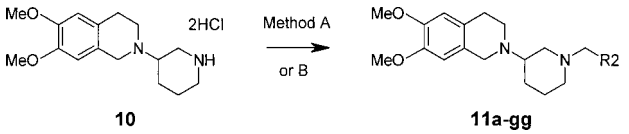
piperidinol (**7**),[23] to yield the 2-(3-piperidyl)-1,2,3,4-tetrahydroisoquinoline derivative **9**. Compound **9** was easily deprotected with HCl/AcOEt to give the key intermediate amine **10**. Compound **10** was converted to compounds **11a**—**gg** by the two general methods illustrated in Chart 2. Reductive alkylation with the corresponding aldehydes in the presence of $NaBH(OAc)_3$ and acetic acid (Method A) of **10** gave compounds **11**. By using a different method (Method B), compound **10** was transformed to compounds **11** by acylation



Conditions: (a) 1-benzylpiperidones (**5a**, **5c**) or 1-benzylpyrrolidone (**5b**), $NaBH(OAc)_3$, AcOH, Et_3N, CH_2Cl_2; (b) $(COCl)_2$, DMSO, CH_2Cl_2, −70 °C, then Et_3N; (c) 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**4a**), $NaBH(OAc)_3$, AcOH, Et_3N, THF; (d) 4 N HCl/AcOEt, MeOH

Chart 1



Method A: $R2CHO$, $NaBH(OAc)_3$, AcOH, Et_3N, CH_2Cl_2
Method B: (a) $R2CO_2H$, EDC·HCl, HOBt, Et_3N, CH_2Cl_2; (b) $LiAlH_4$, THF, reflux

Chart 2

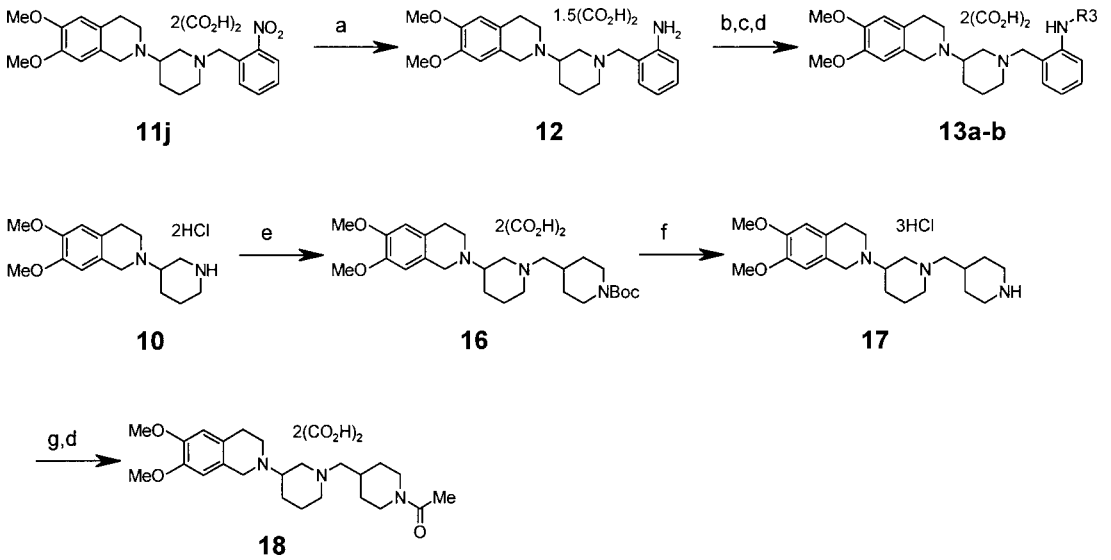
with the corresponding carboxylic acids in the presence of 1-ethyl-3-[3-(diethylamino)propyl]carbodiimide hydrochloride (EDC·HCl) and 1-hydroxybenzotriazole (HOBt) followed by reduction with lithium alminum hydride ($LiAlH_4$). Hydrogenation of the nitro group in **11j** with PtO_2 gave the 2-aminobenzyl derivative **12** (Chart 3). Compound **12** was treated with acetic anhydride or methanesulfonyl chloride in pyridine to give the acetamide derivative (**13a**) and the methanesulfonamide derivative (**13b**, Chart 3). The piperidylmethyl derivatives (**17**, **18**) were prepared as shown in Chart 3. Treatment of the intermediate amine **10** with a *N*-*t*-butoxycarbonyl-4-piperidylcarboxyaldehyde (**15**)[24] in the presence of $NaBH(OAc)_3$ and acetic acid followed by deprotection of the *t*-butoxycarbonyl group afforded compound **17** (Chart 3). Compound **17** was acylated with acetic anhydride in pyridine to give compound **18** (Chart 3).

Pharmacological Results and Discussion

***In Vitro* Tests**[25] The bradycardic activity of the synthesized compounds was assessed by measuring the effect on the spontaneous beating rates in the right atria of a guinea pig. A EC_{30} value which means the concentration of the compounds producing a 30% reduction from the initial spontaneous beating rate was determined by linear regression.

Initially, we investigated the effect of the ring size and the substitution position of the cyclic amine as shown in Table 1. Among them, the 3-piperidyl derivative (**6c**) showed potent activity with a EC_{30} value of 0.83 μM, whereas neither the 4-piperidyl derivative (**6a**) nor the 3-pyrrolidyl derivative (**6b**) showed apparent activity. These results indicated that the 2-(3-piperidyl)-1,2,3,4-tetrahydroisoqunoline skeleton of **6c** is essential to show potent bradycardic activity, and suggested that it might allow the basic nitrogen and the 1,2,3,4-tetrahydroisoquinoline ring to interact with target molecules.

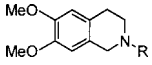
Next, we investigated the effect of the methoxy group on the 1,2,3,4-tetrahydroisoquinoline ring of **6c**. The results are presented in Table 2. Removal of both the 6-methoxy and the 7-methoxy group (**6d**) from **6c** resulted in a complete loss of

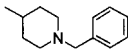
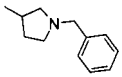
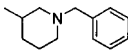


Conditions: (a) H_2, PtO_2, EtOH–H_2O; (b) aq. NaOH; (c) $(MeCO)_2O$ or $MeSO_2Cl$, pyridine; (d) $(CO_2H)_2$; (e) *N*-Boc-4-piperidylcarboxyaldehyde (**15**), $NaBH(OAc)_3$, AcOH, Et_3N, CH_2Cl_2; (f) 4 N HCl/AcOEt, MeOH; (g) $(MeCO)_2O$, Et_3N, CH_2Cl_2

Chart 3

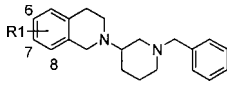
Table 1. Physical Data and Bradycardic Activities of 6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline Derivatives (**6a**—**c**)



Compd.	R	Yield (%)	mp (°C) (Recryst. solvent)	Formula	Analysis (%), Calcd. (Found)				EC_{30} [a] (μM)
					C	H	N	Cl	
6a		78	124—125 (EtOH)	$C_{23}H_{30}N_2O_2$	75.38 (75.27)	8.25 (8.40)	7.64 (7.68)		>10
6b		10	219—221 (EtOH)	$C_{22}H_{28}N_2O_2 \cdot 2HCl$	62.12 (62.13)	7.11 (7.16)	6.59 (6.66)	16.67 (16.48)	>10
6c		25	204—206 (EtOH)	$C_{23}H_{30}N_2O_2 \cdot 2HCl \cdot 0.5H_2O$	61.60 (61.70)	7.42 (7.40)	6.25 (6.24)	15.81 (15.88)	0.83
2									0.27

a) See experimental section, Pharmacology.

Table 2. Physical Data and Bradycardic Activities of 2-(1-Benzyl-3-piperidyl)-1,2,3,4-tetrahydroisoquinoline Derivatives (**6c**—**h**)



Compd.	R1	Yield (%)	mp (°C) (Recryst. solvent)	Formula	Analysis (%), Calcd. (Found)				EC_{30} [a] (μM)
					C	H	N	Cl	
6c	6,7-$(OMe)_2$	[b]	[b]	[b]		[b]			0.83
6d	H	4	209—211 (EtOH)	$C_{21}H_{26}N_2 \cdot 2HCl \cdot 0.8H_2O$	64.05 (64.20)	7.58 (7.47)	7.11 (7.15)	18.01 (17.49)	>10
6e	6-OMe	7	229—235 (MeCN–MeOH)	$C_{22}H_{28}N_2O \cdot 2HCl \cdot 0.1H_2O$	64.26 (64.26)	7.40 (7.43)	6.81 (6.83)	17.24 (16.99)	0.92
6f	7-OMe	22	182—185 (EtOH–AcOEt)	$C_{22}H_{28}N_2O \cdot 2HCl \cdot 0.8H_2O$	62.35 (62.24)	7.52 (7.64)	6.61 (6.57)	16.73 (16.63)	0.57
6g	8-OMe	15	207—212 (MeCN)	$C_{22}H_{28}N_2O \cdot 2HCl \cdot 0.3H_2O$	63.70 (63.59)	7.44 (7.49)	6.75 (6.78)	17.09 (17.13)	2.8
6h	7-NO_2	50	212—215 (MeCN)	$C_{21}H_{25}N_3O_2 \cdot 2HCl \cdot 1.4H_2O$	56.10 (56.19)	6.68 (6.50)	9.35 (9.37)	15.77 (15.44)	2.5

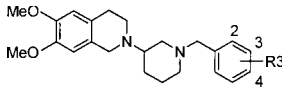
a) See experimental section, Pharmacology. *b*) See Table 1.

activity. On the other hand, removal of only one methoxy group (**6e**, **6f**) from **6c** did not produce any marked effect in potency. Both shifting the methoxy group to the 8-position (**6g**) and converting the methoxy group to a nitro group at 7-position (**6h**) decreased activity by three fold. These results demonstrated that the presence of at least one methoxy group at the 6- or 7-position of the 1,2,3,4-tetrahydroisoquinoline ring is important in inducing potent activity.

Furthermore, we investigated the influence of the substituent on the benzyl group of **6c**, as shown in Table 3. Methoxy (**11a**—**c**), methyl (**11d**—**f**), and chloro groups (**11g**—**i**) were introduced to study the electronic effects. The comparison of **11a**—**i** showed that the order of activity was 2->3->4-substitution and that the chloro group at the 2-position (**11g**) showed the best activity with a EC_{30} value of 0.36 μM. This finding prompted us to introduce another groups at the 2-position. Introduction of cyano (**11k**) and fluoro (**11m**) groups resulted in increases in activity compared to **6c**, whereas nitro (**11j**), trifluoromethyl (**11l**), acetamide (**13a**), methanesulfonamide (**13b**), hydroxy (**11n**) and amino (**12**) derivatives were found to be less effective than **6c**. These results indicated that for groups introduced at the 2-position, it is steric bulkiness or hydrophobicity, rather than the electronic effect of the substituents, which affects the level of activity, and that groups which are less bulky or which have appropriate hydrophobicity are preferable for activity. Among the 2,3-disubstituted derivatives (**11o**—**q**), the dimethoxy (**11o**) and difluoro (**11q**) derivatives were as potent as **6c**.

Finally, we carried out modification of the benzyl moiety in **6c**. The results are shown in Table 4. Replacement of the benzyl group with a cyclohexylmethyl group (**11r**) lowered activity by two fold, and replacement with a 4-piperidylmethyl group (**17**—**18**) resulted in a complete loss of activity. These results indicated that the aromatic ring is preferable to produce potent activity. As alternative substituents for the benzyl group, the heteroarylmethyl derivatives (**11s**—**aa**) were tested. The pyridylmethyl derivatives (**11s**—**u**) showed lower activity than **6c**. Of the five memberd heterocycles (**11v**—**aa**), the 3-methyl-2-thienylmethyl derivative (**11z**) induced the most potent activity with a EC_{30} value of 0.43 μM. The bicyclic and tricyclic derivatives (**11bb**—**gg**) were also evaluated. The 1-naphtylmethyl derivative (**11bb**) was slightly more potent than **6c**. All the nitrogen-containing bi-

Table 3. Physical Data and Bradycardic Activities of 2-(1-Benzyl-3-piperidyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline Derivatives (**6c**, **11a**—**q**, **12**, **13a**, **b**)



Compd.	R3	Method[a)]	Yield (%)	mp (°C) (Recryst. solvent)	Formula	Analysis (%), Calcd. (Found)				EC_{30}[b)] (μM)
						C	H	N	Others	
6c	H	*a)*	*c)*	*c)*	*c)*			*c)*		0.83
11a	2-OMe	A	70	175—177 (EtOH–Et_2O)	$C_{24}H_{32}N_2O_3 \cdot 2HCl \cdot 0.5H_2O$	60.25 (60.23)	7.37 (7.50)	5.85 (5.80)	Cl, 14.82 (15.05)	1.8
11b	3-OMe	A	47	171—173 (EtOH–Et_2O)	$C_{24}H_{32}N_2O_3 \cdot 2HCl \cdot 1.2H_2O$	58.70 (58.71)	7.47 (7.68)	5.70 (5.59)	Cl, 14.44 (14.31)	3.1
11c	4-OMe	A	27	195—197 (MeCN)	$C_{24}H_{32}N_2O_3 \cdot 2HCl \cdot 0.5H_2O$	60.25 (60.28)	7.37 (7.19)	5.85 (5.83)	Cl, 14.82 (15.04)	>10
11d	2-Me	A	78	135—137 (MeCN)	$C_{24}H_{32}N_2O_2 \cdot 2(CO_2H)_2 \cdot 0.3H_2O$	59.42 (59.33)	6.52 (6.54)	4.95 (4.93)		0.68
11e	3-Me	A	31	150—152 (MeCN)	$C_{24}H_{32}N_2O_2 \cdot 1.5(CO_2H)_2 \cdot 0.5H_2O$	61.82 (61.92)	6.92 (6.74)	5.34 (5.34)		1.1
11f	4-Me	A	60	152—154 (MeCN)	$C_{24}H_{32}N_2O_2 \cdot 1.5(CO_2H)_2 \cdot 0.5H_2O$	61.82 (61.51)	6.92 (6.88)	5.34 (5.35)		1.4
11g	2-Cl	A	69	112—115 (MeCN)	$C_{23}H_{29}N_2O_2Cl \cdot 2(CO_2H)_2 \cdot 1.7H_2O$	53.02 (53.08)	6.00 (5.97)	4.58 (4.53)	Cl, 5.80 (5.92)	0.36
11h	3-Cl	A	54	109—113 (MeCN)	$C_{23}H_{29}N_2O_2Cl \cdot 2(CO_2H)_2 \cdot 2H_2O$	52.64 (52.33)	5.89 (5.50)	4.55 (4.40)	Cl, 5.76 (6.01)	0.58
11i	4-Cl	A	64	138—142 (MeCN)	$C_{23}H_{29}N_2O_2Cl \cdot 2(CO_2H)_2$	55.82 (56.14)	5.72 (5.89)	4.82 (5.02)	Cl, 6.10 (6.95)	1.2
11j	2-NO_2	A	79	116—118 (MeOH)	$C_{23}H_{29}N_3O_4 \cdot 2(CO_2H)_2 \cdot H_2O$	53.20 (53.32)	5.79 (5.75)	6.89 (6.80)		1.3
11k	2-CN	A	48	103—110 (MeCN)	$C_{24}H_{29}N_3O_2 \cdot 2(CO_2H)_2 \cdot 1.2H_2O$	56.69 (56.68)	6.01 (5.93)	7.08 (7.05)		0.59
11l	2-CF_3	A	48	120—124 (MeCN)	$C_{24}H_{29}N_2O_2F_3 \cdot 2(CO_2H)_2 \cdot 1.8H_2O$	51.98 (52.02)	5.70 (5.52)	4.33 (4.29)	F, 8.81 (8.89)	1.0
11m	2-F	A	67	118—122 (MeCN)	$C_{23}H_{29}N_2O_2 \cdot 1.5(CO_2H)_2 \cdot H_2O$	58.09 (57.87)	6.37 (6.20)	5.21 (5.24)	F, 3.35 (3.59)	0.73
13a	2-NH COMe	*a)*	67	amorphous	$C_{25}H_{33}N_3O_3 \cdot 2(CO_2H)_2 \cdot 0.2H_2O$	57.36 (57.18)	6.21 (6.39)	6.92 (7.27)		2.3
13b	2-NH SO_2Me	*a)*	49	215—216 (MeOH)	$C_{24}H_{33}N_3O_4S \cdot (CO_2H)_2 \cdot 0.3H_2O$	56.26 (56.23)	6.46 (6.23)	7.57 (7.52)	S, 5.78 (5.94)	3.8
11n	2-OH	A	60	203—204 (MeOH)	$C_{23}H_{30}N_2O_3 \cdot 2(CO_2H)_2$	57.65 (57.47)	6.09 (6.02)	4.98 (5.00)		1.6
12	2-NH_2	*a)*	73	126—134 (MeOH)	$C_{23}H_{31}N_3O_2 \cdot 1.5(CO_2H)_2 \cdot H_2O$	58.42 (58.55)	6.79 (6.59)	7.86 (7.81)		1.5
11o	2,3-$(OMe)_2$	A	49	156—158 (MeCN)	$C_{25}H_{34}N_2O_4 \cdot 2HCl \cdot H_2$	58.03 (57.99)	7.40 (7.75)	5.41 (5.45)	Cl, 13.70 (13.58)	0.83
11p	2,3-(OCH_2O)	A	65	164—166 (MeCN)	$C_{24}H_{30}N_2O_4 \cdot 1.5(CO_2H)_2 \cdot 0.5H_2O$	58.48 (58.32)	6.18 (5.88)	5.05 (5.08)		1.4
11q	2,3-F_2	A	95	126—128 (MeCN)	$C_{23}H_{28}N_2O_2F_2 \cdot 2(CO_2H)_2 \cdot H_2O$	53.68 (53.64)	5.74 (5.65)	4.64 (4.56)	F, 6.29 (6.43)	0.75

a) See experimental section, Chemistry. *b*) See experimental section, Pharmacology. *c*) See Table 1.

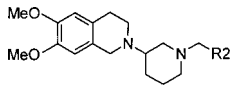
cyclic derivatives (**11cc**—**ff**) showed higher activity than **6c**, except for the 3-indolylmethyl derivative (**11cc**). Particularly, the 4-quinolylmethyl derivative (**11ee**) was shown to be a potent one with a EC_{30} value of 0.37 μM. These results suggested that the nitrogen atom of the bicyclic derivatives may contribute to the improved activity.

***In Vivo* Tests** Compounds with high *in vitro* activities were selected and were examined for their effect on heart rate in urethane-anesthetized rats. The doses of compounds required to produce a 30% decrease of basal values of heart rate are expressed as ED_{30} values. These results are listed in Table 5. Compound **6c** dose-dependently reduced heart rate after intravenous administration with a ED_{30} of 1.4 mg/kg iv, with negligible influence on mean blood pressure (8.4% decrease at 3 mg/kg iv: Fig. 2), although its potency is a half of that of Zatebradine. Compounds **11d**, **11k**, **11o**, **11y**, **11z**, **11bb**, **11ee**, and **11ff** showed moderate *in vivo* activities, whereas compounds **6f**, **11g**, **11q** and **11dd** were not effective in rats, in spite of its potent *in vitro* activities. These results indicated that the 6,7-dimethoxy groups of 1,2,3,4-tetrahydroisoquinoline ring are necessary to exhibit potent *in vivo* activity. These results also suggested that the *in vivo* activity level might be affected by different factors from those in *in vitro* tests, for example, protein binding or distribution.

Conclusions

Novel 1,2,3,4-tetrahydroisoquinoline derivatives bearing directly a cyclic amine at the 2-position were designed and examined for their bradycardic activities in *in vitro* and *in vivo* tests. From their *in vitro* SAR, we obtained the follow-

Table 4. Physical Data and Bradycardic Activities of 2-(3-Piperidyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline Derivatives (**6c**, **11r**—**gg**, **17**, **18**)



Compd.	R2	Method[a]	Yield (%)	mp (°C) (Recryst. solvent)	Formula	Analysis (%), Calcd. (Found)				EC_{30}[b] (μM)
						C	H	N	Others	
6c	Ph	*a*)	*c*)	*c*)	*c*)			*c*)		0.83
11r	cyclohexyl	A	59	128—134 (MeCN)	$C_{23}H_{36}N_2O_2 \cdot 1.5(CO_2H)_2 \cdot 2H_2O$	57.44 (57.47)	7.97 (7.82)	5.15 (5.12)		1.5
17	4-piperidyl	*a*)	80	209—213 (MeOH–AcOEt)	$C_{22}H_{35}N_3O_2 \cdot 3HCl \cdot 1.4H_2O$	52.00 (52.17)	8.09 (8.64)	8.27 (8.11)	Cl, 20.93 (20.44)	>10
18	4-Ac-piperidyl	*a*)	36	115—119 (MeCN–AcOEt)	$C_{24}H_{37}N_3O_3 \cdot 2(CO_2H)_2 \cdot 1.7H_2O$	53.70 (53.78)	7.15 (7.36)	6.71 (6.77)		>10
11s	2-pyridyl	A	26	100—103 (MeCN)	$C_{22}H_{29}N_3O_2 \cdot 2(CO_2H)_2 \cdot 0.8H_2O$	55.57 (55.84)	6.21 (6.65)	7.48 (7.73)		0.95
11t	3-pyridyl	A	34	164—167 (MeCN)	$C_{22}H_{29}N_3O_2 \cdot 3(CO_2H)_2 \cdot 2H_2O$	49.93 (49.86)	5.84 (5.83)	6.24 (6.29)		2.0
11u	4-pyridyl	A	15	173—177 (MeCN)	$C_{22}H_{29}N_3O_2 \cdot 3(CO_2H)_2 \cdot 2H_2O$	49.93 (49.67)	5.84 (5.09)	6.24 (6.24)		1.4
11v	2-thienyl	A	63	132—134 (MeOH)	$C_{21}H_{28}N_2O_2S \cdot 2(CO_2H)_2 \cdot 0.5H_2O$	53.47 (53.54)	5.92 (6.32)	4.99 (5.23)	S, 5.71 (5.84)	0.79
11w	3-thienyl	A	56	126—129 (MeOH)	$C_{21}H_{28}N_2O_2S \cdot 1.5(CO_2H)_2 \cdot 1.2H_2O$	54.47 (54.28)	6.36 (6.42)	5.29 (5.38)	S, 6.06 (5.99)	0.87
11x	2-furyl	A	74	112—115 (MeCN)	$C_{21}H_{28}N_2O_3 \cdot 1.5(CO_2H)_2 \cdot 1.2H_2O$	54.64 (54.37)	6.69 (6.60)	5.31 (5.20)		1.4
11y	3-furyl	A	56	121—123 (MeCN–MeOH)	$C_{21}H_{28}N_2O_3 \cdot 2(CO_2H)_2 \cdot 1.6H_2O$	53.11 (53.17)	6.28 (6.33)	4.95 (5.17)		0.73
11z	3-Me-2-thienyl	B	35	127—129 (MeOH)	$C_{22}H_{30}N_2O_2S \cdot 1.5(CO_2H)_2 \cdot 1.1H_2O$	55.46 (55.36)	6.55 (6.56)	5.17 (5.18)	S, 5.92 (5.94)	0.43
11aa	2-thiazolyl	A	67	117—120 (MeCN)	$C_{20}H_{27}N_3O_2S \cdot 2(CO_2H)_2 \cdot 1.2H_2O$	50.12 (49.97)	5.85 (6.03)	7.31 (7.40)	S, 5.57 (5.67)	1.4
11bb	1-naphtyl	A	76	146—148 (MeCN)	$C_{27}H_{32}N_2O_2 \cdot 1.5(CO_2H)_2 \cdot 0.5H_2O$	64.27 (64.30)	6.47 (6.47)	5.00 (5.04)		0.73
11cc	3-indolyl	A	72	149—153 (MeCN)	$C_{25}H_{31}N_3O_2 \cdot 2(CO_2H)_2 \cdot 0.1H_2O$	59.30 (59.15)	6.04 (6.27)	7.15 (7.30)		1.0
11dd	4-indolyl	B	51	173—175 (MeOH)	$C_{25}H_{31}N_3O_2 \cdot 1.5(CO_2H)_2 \cdot 0.5H_2O$	61.19 (61.09)	6.42 (6.36)	7.65 (7.73)		0.58
11ee	4-quinolyl	A	56	182—186 (MeCN)	$C_{26}H_{31}N_3O_2 \cdot 2(CO_2H)_2$	60.29 (60.15)	5.90 (6.18)	7.03 (7.32)		0.37
11ff	8-quinolyl	B	12	133—136 (MeCN)	$C_{26}H_{31}N_3O_2 \cdot 1.5(CO_2H)_2 \cdot H_2O$	61.04 (61.05)	6.36 (6.64)	7.36 (7.28)		0.55
11gg	2-fluorenyl	A	51	145—146 (MeCN)	$C_{30}H_{34}N_2O_2$	79.26 (79.59)	7.54 (7.42)	6.16 (6.26)		1.6

a) See experimental section, Chemistry. *b*) See experimental section, Pharmacology. *c*) See Table 1.

Table 5. Bradycardic Activities of Selected Compounds in Urethane-Anesthetized Rats

Compd.	ED_{30}[a] (mg/kg iv)
6c	1.4
6f	>10
11d	3.5
11g	>10
11k	3.8
11m	6.2
11o	1.9
11q	>10
11y	3.8
11z	3.7
11bb	3.2
11dd	9.8
11ee	4.4
11ff	2.3
2	0.76

a) See experimental section, Pharmacology.

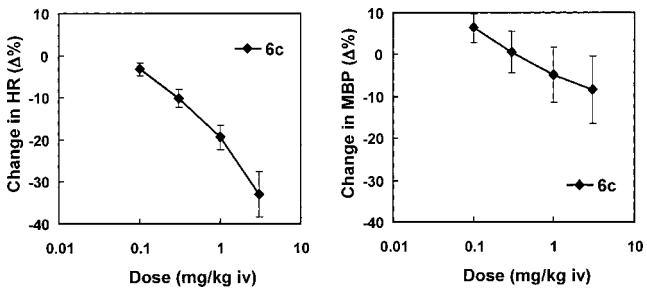


Fig. 2. Effect of **6c** on Heart Rate (HR) and Mean Blood Pressure (MBP) in Urethane-Anesthetized Rats

The values are mean±S.E.M. from three experiments.

ing findings. 1) The 2-(3-piperidyl)-1,2,3,4-tetrahydroisoquinoline skeleton is essential for the appearance of potent activity. 2) The presence of at least one methoxy group at the 6- or 7-position of the 1,2,3,4-tetrahydroisoquinoline ring is

Table 6. Spectral Data for Compounds **11a**—**gg**

Compd.	^{1}H-NMR (DMSO-d_6) δ	MS m/z
11a	(500 MHz) 1.79—1.97 (3H, m), 2.27—2.33 (1H, m), 2.82—3.00 (2H, m), 3.27—3.51 (5H, m), 3.73 (3H, s), 3.75 (3H, s), 3.87 (3H, s), 3.96—4.02 (2H, m), 4.29—4.45 (4H, m), 6.78 (1H, s), 6.82 (1H, s), 7.02 (1H, t, J=7.5 Hz)	397 (M^++1) (FAB)
11b	(500 MHz) 1.79—1.98 (3H, m), 2.31—2.37 (1H, m), 2.85—3.02 (2H, m), 3.22 (2H, br s), 3.36—3.55 (3H, m), 3.73 (3H, s), 3.74 (3H, s), 3.80 (3H, s), 4.00 (2H, br s), 4.29—4.37 (4H, m), 6.79 (1H, s), 6.82 (1H, s), 7.01 (1H, d, J=7.5 Hz), 7.19 (1H, s), 7.34—7.37 (2H, m), 11.89—11.99 (2H, m)	397 (M^++1) (FAB)
11c	(500 MHz) 1.75—2.00 (3H, m), 2.27—2.35 (1H, m), 2.81—3.03 (2H, m), 3.17—3.48 (5H, m), 3.73 (3H, s), 3.74 (3H, s), 3.78 (3H, s), 3.94—4.01 (2H, m), 4.23—4.35 (4H, m), 6.75 (1H, s), 6.82 (1H, s), 7.00 (2H, d, J=8.5 Hz), 7.56 (2H, br s), 11.60—11.77 (2H, m)	397 (M^++1) (FAB)
11d	(400 MHz) 1.51—1.63 (2H, m), 1.82—1.86 (1H, m), 2.01 (1H, br s), 2.28—2.37 (1H, m), 2.34 (3H, s), 2.50 (1H, br s), 2.75—2.78 (1H, m), 2.91—2.92 (2H, m), 3.12—3.15 (1H, m), 3.30 (3H, br s), 3.67 (2H, br s), 3.71 (3H, s), 3.72 (3H, s), 4.13 (2H, br s), 6.68 (1H, s), 6.77 (1H, s), 7.15—7.24 (3H, m), 7.30 (1H, d, J=6.8 Hz)	380 (M^+) (EI)
11e	(400 MHz) 1.57—1.59 (2H, m), 1.84 (1H, br s), 1.97 (1H, br s), 2.32 (3H, s), 2.35 (1H, br s), 2.50—2.56 (1H, m), 2.85 (3H, br s), 3.15 (4H, br s), 3.70 (3H, s), 3.72 (3H, s), 3.75—3.82 (2H, m), 4.01 (2H, br s), 6.67 (1H, s), 6.74 (1H, s), 7.15—7.21 (3H, m), 7.27 (1H, t, J=7.6 Hz)	380 (M^+) (EI)
11f	(400 MHz) 1.56—1.60 (2H, m), 1.83—1.86 (1H, m), 1.98 (1H, br s), 2.31 (3H, s), 2.40 (1H, br s), 2.60 (1H, br s), 2.83 (2H, br s), 2.91 (1H, d, J=11.2 Hz), 3.10—3.21 (4H, m), 3.70 (3H, s), 3.71 (3H, s), 3.85—3.86 (2H, m), 3.96 (2H, s), 6.67 (1H, s), 6.73 (1H, s), 7.20 (2H, d, J=7.6 Hz), 7.29 (2H, d, J=8.0 Hz)	381 (M^++1) (FAB)
11g	(400 MHz) 1.52—1.66 (2H, m), 1.81—1.85 (1H, m), 2.05 (1H, br s), 2.22 (1H, br s), 2.47—2.51 (1H, m), 2.72—2.75 (1H, m), 2.94—2.97 (2H, m), 3.15—3.18 (1H, m), 3.37—3.42 (3H, m), 3.71 (2H, br s), 3.71 (3H, s), 3.74 (3H, s), 4.26 (2H, s), 6.74 (1H, s), 6.79 (1H, s), 7.30—7.37 (2H, m), 7.45 (1H, dd, J=7.2, 2.0 Hz), 7.52 (1H, dd, J=6.8, 2.0 Hz)	401 (M^++1) (FAB)
11h	(400 MHz) 1.57—1.62 (2H, m), 1.82—1.85 (1H, m), 2.01 (1H, br s), 2.22—2.27 (1H, m), 2.47—2.51 (1H, m), 2.73—2.76 (1H, m), 2.93 (2H, br s), 3.10—3.13 (1H, m), 3.34 (3H, br s), 3.72 (3H, s), 3.73 (3H, s), 3.75 (2H, br s), 4.19 (2H, br s), 6.72 (1H, s), 6.78 (1H, s), 7.33—7.34 (1H, m), 7.36—7.42 (2H, m), 7.45 (1H, s)	401 (M^++1) (FAB)
11i	(400 MHz) 1.56—1.58 (2H, m), 1.83 (1H, br s), 2.01 (1H, br s), 2.20—2.25 (1H, m), 2.46—2.50 (1H, m), 2.77—2.80 (1H, m), 2.89—2.92 (2H, m), 3.14—3.16 (1H, m), 3.28 (3H, br s), 3.71 (3H, s), 3.72 (3H, s), 3.74 (2H, br s), 4.13 (2H, br s), 6.71 (1H, s), 6.77 (1H, s), 7.39—7.45 (4H, m)	401 (M^++1) (FAB)
11j	(400 MHz) 1.42—1.57 (2H, m), 1.75—1.79 (1H, m), 2.06—2.11 (2H, m), 2.39 (1H, br s), 2.56—2.58 (1H, m), 2.95 (2H, br s), 3.05 (1H, d, J=10.0 Hz), 3.25 (1H, br s), 3.41 (2H, br s), 3.71 (3H, s), 3.73 (3H, s), 3.83 (2H, s), 4.25 (2H, s), 6.75 (1H, s), 6.79 (1H, s), 7.54 (1H, dt, J=8.4, 2.0 Hz), 7.65—7.71 (2H, m), 7.91 (1H, d, J=7.2 Hz)	412 (M^++1) (FAB)
11k	(400 MHz) 1.50—1.63 (2H, m), 1.80—1.83 (1H, m), 2.06—2.07 (1H, m), 2.17 (1H, br s), 2.45—2.50 (1H, m), 2.66—2.68 (1H, m), 2.96 (2H, br s), 3.12 (1H, br s), 3.36—3.44 (3H, m), 3.70—3.80 (2H, m), 3.72 (3H, s), 3.73 (3H, s), 4.28 (2H, s), 6.75 (1H, s), 6.80 (1H, s), 7.49 (1H, br s), 7.61 (1H, d, J=7.2 Hz), 7.70 (1H, br s), 7.84 (1H, d, J=7.2 Hz)	392 (M^++1) (FAB)
11l	(400 MHz) 1.58—1.61 (2H, m), 1.81—1.84 (1H, m), 2.07—2.13 (2H, m), 2.40—2.50 (1H, m), 2.64—2.67 (1H, m), 2.97 (2H, br s), 3.11—3.14 (1H, m), 3.39 (3H, br s), 3.71 (3H, s), 3.72 (2H, br s), 3.73 (3H, s), 4.29 (2H, br s), 6.75 (1H, s), 6.80 (1H, s), 7.49 (1H, br s), 7.68 (1H, br s), 7.72 (1H, d, J=8.0 Hz), 7.80 (1H, d, J=8.0 Hz)	435 (M^++1) (FAB)
11m	(400 MHz) 1.54—1.56 (2H, m), 1.83 (1H, br s), 2.01 (1H, br s), 2.22 (1H, br s), 2.45—2.50 (1H, m), 2.75—2.77 (1H, m), 2.92 (2H, br s), 3.15—3.17 (1H, m), 3.34 (3H, br s), 3.71 (3H, s), 3.72 (3H, s), 3.73 (2H, br s), 4.18 (2H, br s), 6.72 (1H, s), 6.78 (1H, s), 7.19—7.23 (2H, m), 7.35—7.40 (1H, m), 7.44—7.48 (1H, m)	368 (M^++1) (FAB)
11n	(400 MHz) 1.60—1.65 (2H, m), 1.87—1.90 (1H, m), 1.95—1.97 (1H, m), 2.58—2.60 (1H, m), 2.76—2.81 (3H, m), 3.03—3.05 (3H, m), 3.15 (1H, br s), 3.32 (1H, d, J=10.8 Hz), 3.70 (3H, s), 3.71 (3H, s), 3.91 (2H, br s), 3.99 (2H, s), 6.65 (1H, s), 6.72 (1H, s), 6.83 (1H, br s), 6.89 (1H, d, J=7.6 Hz), 7.21 (1H, br s), 7.29 (1H, dd, J=7.6, 1.2 Hz)	383 (M^++1) (FAB)
11o	(500 MHz) 1.79—1.97 (3H, m), 2.27 (1H, br s), 2.84—2.95 (2H, m), 3.23—3.40 (5H, m), 3.73 (3H, s), 3.74 (3H, s), 3.82 (3H, s), 3.84 (3H, s), 3.98 (2H, br s), 4.31—4.44 (4H, m), 6.77 (1H, s), 6.82 (1H, s), 7.12—7.16 (3H, m), 7.33 (1H, br s), 11.50—11.81 (2H, m)	427 (M^++1) (FAB)
11p	(500 MHz) 1.55—1.56 (2H, m), 1.83 (1H, br s), 1.97 (1H, br s), 2.27 (1H, br s), 2.49 (1H, br s), 2.79 (1H, br s), 2.90 (2H, br s), 3.14—3.16 (1H, m), 3.27 (3H, br s), 3.68—3.70 (2H, m), 3.71 (3H, s), 3.72 (3H, s), 4.12 (2H, s), 6.01 (2H, s), 6.70 (1H, s), 6.77 (1H, s), 6.83—6.89 (3H, m)	411 (M^++1) (FAB)
11q	(400 MHz) 1.53—1.59 (2H, m), 1.83 (1H, br s), 2.01 (1H, br s), 2.12—2.17 (1H, m), 2.40—2.47 (1H, m), 2.70—2.72 (1H, m), 2.95 (2H, br s), 3.10—3.12 (1H, m), 3.33—3.40 (3H, m), 3.72 (3H, s), 3.73 (3H, s), 3.71—3.73 (2H, m), 4.24 (2H, s), 6.74 (1H, s), 6.80 (1H, s), 7.19—7.29 (2H, m), 7.35—7.41 (1H, m)	403 (M^++1) (FAB)
11r	(400 MHz) 0.86—0.95 (2H, m), 1.08—1.36 (3H, m), 1.53—1.73 (8H, m), 1.85—1.88 (1H, m), 1.97 (1H, br s), 2.50—2.64 (1H, m), 2.66—2.75 (3H, m), 2.81 (2H, br s), 3.04 (2H, br s), 3.13—3.16 (2H, m), 3.34 (1H, br s), 3.70 (3H, s), 3.71 (3H, s), 3.91 (2H, s), 6.67 (1H, s), 6.72 (1H, s)	373 (M^++1) (FAB)
11s	(400 MHz) 1.57—1.62 (2H, m), 1.85 (1H, br s), 2.00 (1H, br s), 2.39 (1H, br s), 2.64 (1H, br s), 2.89 (3H, br s), 3.18—3.24 (4H, m), 3.71 (3H, s), 3.72 (3H, s), 3.90 (2H, s), 4.09 (2H, s), 6.70 (1H, s), 6.76 (1H, s), 7.34 (1H, dd, J=10.8, 6.0 Hz), 7.48 (1H, d, J=7.2 Hz), 7.82 (1H, br s), 8.55 (1H, d, J=5.2 Hz)	368 (M^++1) (FAB)
11t	(400 MHz) 1.56—1.62 (2H, m), 1.85 (1H, br s), 2.02 (1H, br s), 2.21—2.25 (1H, m), 2.48—2.51 (1H, m), 2.73—2.76 (1H, m), 2.94 (2H, br s), 3.11—3.14 (1H, m), 3.37 (3H, br s), 3.69—3.78 (2H, m), 3.72 (3H, s), 3.73 (3H, s), 4.21 (2H, br s), 6.73 (1H, s), 6.79 (1H, s), 7.41 (1H, br s), 7.78 (1H, d, J=8.0 Hz), 8.53 (1H, br s), 8.58 (1H, br s)	368 (M^++1) (FAB)
11u	(400 MHz) 1.54—1.62 (2H, m), 1.81—1.84 (1H, m), 2.05—2.07 (1H, m), 2.14—2.19 (1H, m), 2.42—2.47 (1H, m), 2.68—2.71 (1H, m), 2.96 (2H, br s), 3.09—3.12 (1H, m), 3.40—3.41 (3H, m), 3.62—3.72 (2H, m), 3.72 (3H, s), 3.73 (3H, s), 4.28 (2H, br s), 6.75 (1H, s), 6.80 (1H, s), 7.38 (2H, d, J=4.8 Hz), 8.55 (2H, d, J=2.4 Hz)	368 (M^++1) (FAB)
11v	(400 MHz) 1.55 (2H, br s), 1.83 (1H, br s), 2.02 (1H, br s), 2.20 (1H, br s), 2.44 (1H, br s), 2.82 (1H, br s), 2.91—2.93 (2H, m), 3.18—3.30 (4H, m), 3.70 (3H, s), 3.71 (3H, s), 3.91 (2H, br s), 4.15 (2H, s), 6.72 (1H, s), 6.77 (1H, s), 7.02 (1H, dd, J=5.2, 3.6 Hz), 7.06 (1H, d, J=2.8 Hz), 7.50 (1H, dd, J=5.2, 1.6 Hz)	373 (M^++1) (FAB)
11w	(400 MHz) 1.54—1.62 (2H, m), 1.84—1.87 (1H, m), 1.95—1.98 (1H, m), 2.41 (1H, br s), 2.61 (1H, br s), 2.83 (2H, br s), 2.94 (1H, br s), 3.11—3.24 (4H, m), 3.71 (3H, s), 3.71 (3H, s), 3.93 (2H, s), 3.97 (2H, s), 6.67 (1H, s), 6.73 (1H, s), 7.16 (1H, d, J=4.8 Hz), 7.54 (1H, d, J=3.2 Hz), 7.58 (1H, dd, J=5.2, 3.2 Hz)	373 (M^++1) FAB)

Table 6. Continued

Compd.	^{1}H-NMR (DMSO-d_6) δ	MS m/z
11x	(400 MHz) 1.54 (2H, br s), 1.81 (1H, br s), 1.99 (1H, br s), 2.24 (1H, br s), 2.45—2.50 (1H, m), 2.78 (1H, br s), 2.91 (2H, br s), 3.13 (1H, br s), 3.23—3.29 (3H, m), 3.72 (3H, s), 3.73 (3H, s), 3.75 (2H, d, J=5.2 Hz), 4.13 (2H, s), 6.41 (1H, d, J=3.2 Hz), 6.46 (1H, t, J=2.4 Hz), 6.72 (1H, s), 6.77 (1H, s), 7.65 (1H, s)	357 (M^++1) (FAB)
11y	(400 MHz) 1.51—1.59 (2H, m), 1.81—1.84 (1H, m), 2.01 (1H, br s), 2.18 (3H, s), 2.23 (1H, br s), 2.44 (1H, br s), 2.82 (1H, br s), 2.91 (1H, br s), 3.19—3.29 (4H, m), 3.71 (3H, s), 3.72 (3H, s), 3.81 (2H, s), 4.14 (2H, s), 6.71 (1H, s), 6.76 (1H, s), 6.87 (1H, d, J=5.2 Hz), 7.39 (1H, d, J=5.2 Hz)	357 (M^++1) (FAB)
11z	(400 MHz) 1.57—1.59 (2H, m), 1.84 (1H, br s), 1.97 (1H, br s), 2.32 (3H, s), 2.35 (1H, br s), 2.50—2.56 (1H, m), 2.85 (3H, br s), 3.15 (4H, br s), 3.70 (3H, s), 3.72 (3H, s), 3.93 (2H, s), 3.75—3.78 (2H, m), 4.01 (2H, br s), 6.67 (1H, s), 6.74 (1H, s), 7.15—7.21 (3H, m), 7.27 (1H, t, J=7.6 Hz)	387 (M^++1) (FAB)
11aa	(400 MHz) 1.55 (2H, br s), 1.84 (1H, br s), 2.09 (1H, br s), 2.21 (1H, br s), 2.47 (1H, br s), 2.81 (1H, br s), 2.96 (2H, br s), 3.24 (1H, br s), 3.33 (1H, br s), 3.42 (2H, br s), 3.71 (3H, s), 3.73 (3H, s), 3.96 (2H, s), 4.26 (2H, s), 6.75 (1H, s), 6.79 (1H, s), 7.69 (1H, d, J=2.8 Hz), 7.75 (1H, d, J=3.6 Hz)	374 (M^++1) (FAB)
11bb	(400 MHz) 1.48—1.62 (2H, m), 1.80—1.84 (1H, m), 2.03—2.07 (1H, br s), 2.29 (1H, br s), 2.54 (1H, br s), 2.81 (1H, br s), 2.89 (2H, br s), 3.25—3.30 (4H, m), 3.71 (3H, s), 3.72 (3H, s), 4.04—4.14 (4H, m), 6.65 (1H, s), 6.76 (1H, s), 7.47—7.58 (4H, m), 7.89 (1H, d, J=8.0 Hz), 7.95 (1H, dd, J=6.8, 2.4 Hz), 8.27 (1H, dd, J=8.0, 2.0 Hz)	417 (M^++1) (FAB)
11cc	(400 MHz) 1.53—1.68 (2H, m), 1.89 (2H, br s), 2.73—3.04 (7H, m), 3.25 (1H, br s), 3.48 (1H, br s), 3.69 (3H, s), 3.70 (3H, s), 3.75 (2H, s), 4.37 (2H, br s), 6.60 (1H, s), 6.67 (1H, s), 7.09 (1H, dt, J=6.8, 1.2 Hz), 7.15 (1H, br s), 7.44 (1H, d, J=8.4 Hz), 7.57 (1H, d, J=2.4 Hz), 7.76 (1H, d, J=7.6 Hz), 11.48 (1H, s)	406 (M^++1) (FAB)
11dd	(400 MHz) 1.58—1.62 (2H, m), 1.85—1.95 (2H, m), 2.59 (1H, br s), 2.78 (3H, br s), 3.01 (3H, br s), 3.12 (1H, br s), 3.33 (1H, br s), 3.70 (3H, s), 3.71 (3H, s), 3.88 (2H, s), 4.22 (2H, br s), 6.61 (1H, s), 6.69—6.70 (2H, m), 7.10—7.13 (2H, m), 7.40—7.44 (2H, m), 11.28 (1H, br s)	406 (M^++1) (FAB)
11ee	(400 MHz) 1.52—1.63 (2H, m), 1.82—1.85 (1H, m), 2.08 (1H, br s), 2.24 (1H, br s), 2.46 (1H, br s), 2.79 (1H, br s), 2.93 (2H, br s), 3.22 (1H, br s), 3.36—3.41 (3H, m), 3.71 (3H, s), 3.73 (3H, s), 4.06 (2H, s), 4.24 (2H, s), 6.70 (1H, s), 6.78 (1H, s), 7.53 (1H, d, J=4.4 Hz), 7.64 (1H, br s), 7.77 (1H, br s), 8.05 (1H, br s), 8.27 (1H, br s), 8.87 (1H, d, J=4.4 Hz)	418 (M^++1) (FAB)
11ff	(400 MHz) 1.57—1.65 (2H, m), 1.78 (1H, br s), 1.85 (1H, br s), 1.97 (1H, br s), 2.69—2.89 (4H, m), 3.11—3.26 (2H, m), 3.56—3.66 (2H, m), 3.70 (3H, s), 3.72 (3H, s), 3.93—4.18 (3H, m), 4.61 (1H, br s), 5.62—6.24 (1H, m), 6.42 (1H, br s), 6.63—6.87 (3H, m), 7.59—7.67 (1H, m), 7.93—8.03 (1H, m), 8.44—8.92 (1H, m)	418 (M^++1) (FAB)
11gg	(400 MHz) 1.23—1.31 (1H, m), 1.43—1.52 (1H, m), 1.68—1.72 (1H, m), 1.86—1.91 (2H, m), 1.94—1.99 (1H, m), 2.55—2.78 (6H, m), 2.96—2.99 (1H, m), 3.54 (2H, s), 3.59 (2H, s), 3.66 (3H, s), 3.68 (3H, s), 3.90 (2H, s), 6.57 (1H, s), 6.60 (1H, s), 7.27—7.39 (3H, m), 7.51 (1H, s), 7.57 (1H, d, J=7.2 Hz), 7.82—7.87 (2H, m)	455 (M^++1) (FAB)

important to exert potent activity. 3) Replacement of the benzene ring in the benzyl group with a nitrogen-containing bicyclic ring improved activity. *In vivo* tests of selected compounds demonstrated that compound **6c** exhibited potent bradycardic activity with negligible influence on mean blood pressure in rats, although its potency is a half of that of Zatebradine. From these results, we have identified the 2-(3-piperidyl)-1,2,3,4-tetrahydroisoquinoline derivatives including **6c** as a specific bradycardic agents possessing a novel skeleton.

Further research to obtain specific bradycardic agent with superior properties is in progress and will be described in a forthcoming paper.

Experimental

All melting points were measured with a Yanaco MP-500D melting point apparatus without correction. ^{1}H-NMR spectra were obtained on a JEOL JNM-LA300 or a JNM-EX400 or a JNM-GX500 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; 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).

Chemistry. 2-(1-Benzyl-4-piperidyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (6a) A suspension of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (**4a**, 3.00 g, 12.7 mmol) in CH_2Cl_2 (30 ml) was treated with Et_3N (1.77 ml, 12.7 mmol), and the mixture was stirred for 10 min at room temperature. To the mixture were added 1-benzyl-4-piperidone (**5a**, 2.51 g, 13.3 mmol), acetic acid (1.81 ml, 31.7 mmol) and sodium acetoxyborohydride ($NaBH(OAc)_3$) (3.12 g, 15.2 mmol), and the mixture was stirred for 2 h at room temperature. The mixture was made alkaline with 1 N aqueous NaOH and was extracted with $CHCl_3$ (30 ml×2). The combined extract was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was crystallized from EtOH to give **9** (3.61 g, 78%) as a colorless powder. mp 124—125 °C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.68—1.73 (2H, m), 1.85—1.87 (2H, m), 2.01 (2H, t, J=11.0 Hz), 2.44—2.48 (1H, m), 2.80—2.81 (4H, m), 2.97 (2H, d, J=12.0 Hz), 3.51 (2H, s), 3.70 (2H, s), 3.82 (3H, s), 3.83 (3H, s), 6.51 (1H, s), 6.58 (1H, s), 7.23—7.25 (2H, m), 7.30—7.32 (3H, m). FAB-MS m/z: 367 (M^++1). *Anal.* Calcd for $C_{23}H_{30}N_2O_2$: C, 75.38; H, 8.25; N, 7.64. Found: C, 7 5.27; H, 8.40; N, 7.68.

2-(1-Benzyl-3-pyrrolidyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline Dihydrochroride (6b) The title compound was prepared in the same manner as described for **6a** using 1-benzyl-3-pyrrolidone (**5b**) instead of **5a**, in 10% yield. mp 219—221 °C. ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 2.37—2.62 (4H, m), 2.91 (1H, br s), 3.15—3.32 (2H, m), 3.48 (3H, br s), 3.62—3.88 (1H, m), 3.72 (3H, s), 3.74 (3H, s), 4.17—4.51 (4H, m), 6.75—6.82 (2H, m), 7.46 (3H, s), 7.62—7.68 (2H, m). FAB-MS m/z: 353 (M^++1). *Anal.* Calcd for $C_{22}H_{28}N_2O_2 \cdot 2HCl$: C, 62.12; H, 7.11; N, 6.59; Cl, 16.67. Found: C, 62.13; H, 7.16; N, 6.66; Cl, 16.48.

2-(1-Benzyl-3-piperidyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline Dihydrochloride (6c) The title compound was prepared in the same manner as described for **6a** using 1-benzyl-3-piperidone (**5c**) instead of **5a**, in 25% yield. mp 219—221 °C. ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 1.76—1.98 (3H, m), 2.27—2.35 (1H, m), 2.84—3.01 (2H, m), 3.15—3.36 (5H, m), 3.73 (3H, s), 3.75 (3H, s), 3.93 (2H, br s), 4.35 (4H, br s), 6.77 (1H, s), 6.82 (1H, s), 7.47 (3H, br s), 7.65 (2H, br s), 11.56—11.70 (2H, m). FAB-MS m/z: 367 (M^++1). *Anal.* Calcd for $C_{23}H_{30}N_2O_2 \cdot 2HCl \cdot 0.5H_2O$: C, 61.60; H, 7.42; N, 6.25; Cl, 15.81. Found: C, 61.70; H, 7.40; N, 6.24; Cl, 15.88.

2-(1-Benzyl-3-piperidyl)-1,2,3,4-tetrahydroisoquinoline Dihydrochloride (6d) The title compound was prepared in the same manner as described for **6a** using 1,2,3,4-tetrahydroisoquinoline (**4b**) and **5c** instead of **4a** and **5a**, in 4% yield. mp 209—211 °C. ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 1.78—1.99 (3H, m), 2.29 (1H, br s), 2.86 (1H, br s), 3.06 (1H, br s), 3.27—3.42 (5H, m), 3.94 (2H, br s), 4.35—4.49 (4H, m), 7.20—7.28 (4H, m), 7.46 (3H, br s), 7.65 (2H, br s), 11.60—11.75 (2H, m). FAB-MS m/z: 307 (M^++1). *Anal.* Calcd for $C_{21}H_{26}N_3 \cdot 2HCl \cdot 0.8H_2O$: C, 64.05; H, 7.58; N, 7.11; Cl, 18.01. Found: C, 64.20; H, 7.47; N, 7.15; Cl, 17.49.

2-(1-Benzyl-3-piperidyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline Dihydrochloride (6e) The title compound was prepared in the same manner as described for **6a** using 6-methoxy-1,2,3,4-tetrahydroisoquinoline (**4c**)[18] and **5c** instead of **4a** and **5a**, in 7% yield. mp 229—235 °C. ^{1}H-NMR

(400 MHz, DMSO-d_6) δ: 1.68—1.97 (3H, m), 2.28 (1H, br s), 2.86—3.64 (7H, m), 3.75 (3H, s), 3.94 (2H, br s), 4.36 (4H, br s), 6.82 (1H, s), 6.86 (1H, d, J=8.0 Hz), 7.12 (1H, d, J=8.8 Hz), 7.46 (3H, s), 7.66 (2H, s), 11.68—11.80 (2H, m). EI-MS m/z: 336 (M^+). *Anal.* Calcd for $C_{22}H_{28}N_2O_2 \cdot 2HCl \cdot 0.1H_2O$: C, 64.26; H, 7.40; N, 6.81; Cl, 17.24. Found: C, 64.26; H, 7.43; N, 6.83; Cl, 16.99.

2-(1-Benzyl-3-piperidyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline Dihydrochloride (6f) The title compound was prepared in the same manner as described for **6a** using 7-methoxy-1,2,3,4-tetrahydroisoquinoline (**4d**)[18] and **5c** instead of **4a** and **5a**, in 22% yield. mp 182—185 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.79—1.99 (3H, m), 2.31 (1H, br s), 2.85—3.45 (7H, m), 3.74 (3H, s), 3.97 (2H, br s), 4.36—4.43 (4H, m), 6.78 (1H, br s), 6.88 (1H, d, J=5.6 Hz), 7.16 (1H, d, J=8.1 Hz), 7.46—7.47 (3H, m), 7.66 (2H, br s), 11.88 (2H, br s). FAB-MS m/z: 337 (M^++1). *Anal.* Calcd for $C_{22}H_{28}N_2O_2 \cdot 2HCl \cdot 0.8H_2O$: C, 62.35; H, 7.54; N, 6.61; Cl, 16.73. Found: C, 62.24; H, 7.64; N, 6.57; Cl, 16.63.

2-(1-Benzyl-3-piperidyl)-8-methoxy-1,2,3,4-tetrahydroisoquinoline Dihydrochloride (6g) The title compound was prepared in the same manner as described for **6a** using 8-methoxy-1,2,3,4-tetrahydroisoquinoline (**4e**)[18] and **5c** instead of **4a** and **5a**, in 15% yield. mp 207—212 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.88—1.97 (3H, m), 2.30 (1H, br s), 2.88—2.99 (2H, m), 3.26—3.33 (3H, m), 3.60 (1H, br s), 3.83 (3H, s), 4.01 (1H, br s), 4.20—4.36 (6H, m), 6.83 (1H, d, J=7.6 Hz), 6.93 (1H, d, J=8.0 Hz), 7.27 (1H, t, J=7.6 Hz), 7.46—7.47 (3H, m), 7.66 (2H, s), 11.68—11.80 (2H, m). FAB-MS m/z: 337 (M^++1). *Anal.* Calcd for $C_{22}H_{28}N_2O_2 \cdot 2HCl \cdot 0.3H_2O$: C, 63.70; H, 7.44; N, 6.75; Cl, 17.09. Found: C, 63.59; H, 7.49; N, 6.78; Cl, 17.13.

2-(1-Benzyl-3-piperidyl)-7-nitro-1,2,3,4-tetrahydroisoquinoline Dihydrochloride (6h) The title compound was prepared in the same manner as described for **6a** using 7-nitro-1,2,3,4-tetrahydroisoquinoline (**4f**)[19] and **5c** instead of **4a** and **5a**, in 50% yield. mp 212—215 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.78—2.02 (4H, m), 2.33 (1H, br s), 2.67 (1H, br s), 3.25—3.33 (4H, m), 3.70 (2H, br s), 3.95 (1H, br s), 4.34—4.37 (2H, m), 4.59 (2H, br s), 7.46—7.47 (3H, m), 7.50—7.56 (1H, m), 7.66 (2H, s), 8.13—8.17 (2H, m), 11.70—12.00 (2H, m). FAB-MS m/z: 352 (M^++1). *Anal.* Calcd for $C_{21}H_{25}N_3O_2 \cdot 2HCl \cdot 1.4H_2O$: C, 56.10; H, 6.68; N, 9.35; Cl, 15.77. Found: C, 56.19; H, 6.50; N, 9.37; Cl, 15.44.

6,7-Dimethoxy-2-(3-piperidyl)-1,2,3,4-tetrahydroisoquinoline Dihydrochloride (10) 1) To a solution of oxalyl chloride (4.72 ml, 55.0 mmol) in CH_2Cl_2 (50 ml) was added dropwise a solution of dimethylsulfoxide (4.88 ml, 68.8 mmol) in CH_2Cl_2 (10 ml) at −70 °C, and the mixture was stirred for 10 min at −70 °C. To the mixture was added dropwise a solution of **7** (5.88 g, 27.5 mmol) in CH_2Cl_2 (15 ml) at −70 °C, and the mixture was stirred for 1 h at −70 °C. To the mixture was added Et_3N (15.3 ml, 110 mmol) at −70 °C, and the mixture was stirred for 1 h at 0 °C. To the mixture was added 2 N aqueous NH_4Cl (55 ml), and the whole was partitioned between $CHCl_3$ (30 ml×2) and H_2O (50 ml). The combined $CHCl_3$ layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give crude **8**. Then a suspension of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (**4a**, 5.74 g, 25.0 mmol) in tetrahydrofuran (60 ml) was treated with Et_3N (3.48 ml, 25.0 mmol), and the mixture was stirred for 10 min at room temperature. To the mixture were added crude **8**, acetic acid (1.43 ml, 25.0 mmol) and $NaBH(OAc)_3$ (5.83 g, 27.5 mmol), and the mixture was stirred for 5 h at room temperature. The mixture was made alkaline with 1 N aqueous NaOH and was extracted with AcOEt (30 ml×2). The combined extract was washed with saturated NaCl (50 ml) and dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography ($CHCl_3$·MeOH=49/1, v/v) to give **9** (7.76 g, 82%) as a yellow syrup. 2) To a solution of **9** (7.76 g, 20.6 mmol) in MeOH (30 ml) was added 4 N HCl/AcOEt (25.7 ml) at 0 °C, and the mixture was stirred for 7 h at room temperature. The mixture was concentrated *in vacuo* and residual solid was recrystallized from EtOH–MeOH to give **10** (3.60 g, 50%) as a beige powder. mp 205—216 °C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 1.75—1.86 (2H, m), 1.96—2.00 (1H, m), 2.27 (1H, br s), 2.81—2.94 (2H, m), 3.22—3.40 (5H, m), 3.72 (2H, br s), 3.73 (3H, s), 3.74 (3H, s), 4.34 (2H, br s), 6.78 (1H, s), 6.82 (1H, s), 9.56 (1H, br s), 9.89 (1H, br s), 11.75 (1H, br s). FAB-MS m/z: 277 (M^++1). *Anal.* Calcd for $C_{16}H_{24}N_2O_2 \cdot 2HCl$: C, 55.02; H, 7.50; N, 8.02; Cl, 20.30. Found: C, 54.79; H, 7.55; N, 7.99; Cl, 20.16.

6,7-Dimethoxy-2-[1-(2-nitrobenzyl)-3-piperidyl]-1,2,3,4-tetrahydroisoquinoline Dioxalate (11j, Method A) A suspension of **10** (1.05 g, 3.00 mmol) in CH_2Cl_2 (20 ml) was treated with Et_3N (0.836 ml, 6.00 mmol), and the mixture was stirred for 10 min at room temperature. To the mixture were added 2-nitrobenzaldehyde (0.453 g, 3.00 mmol), acetic acid (0.172 ml, 3.00 mmol) and $NaBH(OAc)_3$ (0.699 g, 3.30 mmol), and the mixture was stirred for 13 h at room temperature. The mixture was made alkaline with 1 N aqueous NaOH and was extracted with $CHCl_3$ (30 ml×2). The combined extract was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography ($CHCl_3$/MeOH=24/1, /v) to give 6,7-dimethoxy-2-[1-(2-nitrobenzyl)-3-piperidyl]-1,2,3,4-tetrahydroisoquinoline (1.47 g, quantitative) as a yellow syrup. This compound was converted to corresponding oxalate and recrystallized from MeOH to give **11j** (1.40 g, 79%) as a colorless powder. mp 116—118 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.42—1.57 (2H, m), 1.75—1.79 (1H, m), 2.06—2.11 (2H, m), 2.39 (1H, br s), 2.56—2.58 (1H, m), 2.95 (2H, br s), 3.05 (1H, br s), 3.25 (1H, br s), 3.41 (2H, br s), 3.71 (3H, s), 3.73 (3H, s), 3.83 (2H, s), 4.25 (2H, s), 6.75 (1H, s), 6.79 (1H, s), 7.54 (1H, dt, J=8.4, 2.0 Hz), 7.65—7.71 (2H, m), 7.91 (1H, d, J=7.2 Hz) FAB-MS m/z: 412 (M^++1). *Anal.* Calcd for $C_{23}H_{29}N_3O_4 \cdot 2(CO_2H)_2 \cdot H_2O$: C, 53.20; H, 5.79; N, 6.89. Found: C, 53.32; H, 5.75; N, 6.80.

6,7-Dimethoxy-2-{1-[(4-indolyl)methyl]-3-piperidyl}-1,2,3,4-tetrahydroisoquinoline Sesquioxalate (11dd, Method B) 1) A suspension of **10** (0.349 g,1.00 mmol) in CH_2Cl_2 (10 ml) was treated with Et_3N (0.279 ml, 2.00 mmol), and the mixture was stirred for 10 min at room temperature. To the mixture were added HOBt (0.068 g, 0.50 mmol), EDC·HCl (0.230 g, 1.20 mmol) and indol-4-carboxylic acid (0.161 g, 1.00 mmol), and the mixture was stirred for 13 h at room temperature. The mixture was partitioned between $CHCl_3$ (15 ml×2) and 0.2 N aqueous NaOH (30 ml). The combined extract was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography ($CHCl_3$/MeOH=24/1, v/v) to give 6,7-dimethoxy-2-{1-[(4-indolyl)carbonyl]-3-piperidyl}-1,2,3,4-tetrahydroisoquinoline (0.390 g, 93%) as a yellow foam. 2) To a suspension of $LiAlH_4$ (0.069 g, 1.8 mmol) in tetrahydrofuran (5 ml) was added a solution of 6,7-dimethoxy-2-{1-[(4-indolyl)carbonyl]-3-piperidyl}-1,2,3,4-tetrahydroisoquinoline (0.380 g, 0.906 mmol) in tetrahydrofuran (5 ml), and the mixture was stirred for 1 h under reflux, then cooled to room temperature. To the mixture was added H_2O (3 ml) at −40 °C, and the mixture was stirred for 1 h at room temperature. The resulting suspension was filtered through Celite pad and the filtrate was partitioned between AcOEt (15 ml×2) and saturated NaCl (30 ml). The combined AcOEt layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography ($CHCl_3$/MeOH=24/1, v/v) to give 6,7-dimethoxy-2-{1-[(4-indolyl)-methyl]-3-piperidyl}-1,2,3,4-tetrahydroisoquinoline (0.321 g, 87%) as a colorless foam. This compound was converted to corresponding oxalate and recrystallized from MeOH to give **11dd** (0.290 g, 55%) as a colorless powder. mp 173—175 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.58—1.62 (2H, m), 1.85—1.95 (2H, m), 2.59 (1H, br s), 2.78 (3H, br s), 3.01 (3H, br s), 3.12 (1H, br s), 3.33 (1H, br s), 3.70 (3H, s), 3.71 (3H, s), 3.88 (2H, s), 4.22 (2H, br s), 6.61 (1H, s), 6.69—6.70 (2H, m), 7.10—7.13 (2H, m), 7.40—7.44 (2H, m), 11.28 (1H, br s). FAB-MS m/z: 406 (M^++1). *Anal.* Calcd for $C_{25}H_{31}N_3O_2 \cdot 1.5(CO_2H)_2 \cdot 0.5H_2O$: C, 61.19; H, 6.42; N, 7.65. Found: C, 61.09; H, 6.36; N, 7.73.

Compounds **11a**—**i**, **11k**—**cc** and **11ee**—**gg** were prepared in the same manner as described above (Method A or B). Their isolated yield, melting points, elemental analyses and yields are listed in Table 3—4, and their ^{1}H-NMR and MS data in Table 6.

2-[1-(2-Aminobenzyl)-3-piperidyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline Sesquioxalate (12) A suspension of **11j** (1.28 g, 2.16 mmol) and PtO_2 (0.022 g) in EtOH–H_2O (3 : 2, 25 ml) was stirred under hydrogen atmosphere for 2 h at room temperature. The mixture was filtered through Celite pad and the filtrate was concentrated *in vacuo*. The residue was made alkaline with 1 N aqueous NaOH and was extracted with $CHCl_3$ (30 ml×2). The combined extract was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography ($CHCl_3$/MeOH=24/1, v/v) to give 2-[1-(3-Aminobenzyl)-3-piperidyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (0.836 g, quantitative) as a yellow syrup. This compound was converted to corresponding oxalate and recrystallized from MeOH to give **12** (0.886 g, 73%) as a colorless powder. mp 126—134 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.57—1.59 (2H, m), 1.82—1.84 (1H, m), 1.99 (1H, br s), 2.35 (1H, br s), 2.56 (1H, br s), 2.86 (3H, br s), 3.17 (4H, br s), 3.63—3.74 (2H, m), 3.71 (3H, s), 3.72 (3H, s), 4.03 (2H, s), 6.54 (1H, dt, J=7.2, 0.8 Hz), 6.66—6.69 (2H, m), 6.74 (1H, s), 7.03—7.06 (2H, m). FAB-MS m/z: 382 (M^++1). *Anal.* Calcd for $C_{23}H_{31}N_3O_2 \cdot 1.5(CO_2H)_2 \cdot H_2O$: C, 58.42; H, 6.79; N, 7.86. Found: C, 58.55; H, 6.59; N, 7.81.

2-{[3-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)piperidino]-methyl}acetanilide Dioxalate (13a) A solution of **12** (1.06 g, 1.89 mmol)

in H_2O (10 ml) was made alkaline with 1 N aqueous NaOH and was extracted with $CHCl_3$ (20 ml×2). The combined extract was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give 2-[1-(3-aminobenzyl)-3-piperidyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (0.722 g, quantitative). To a solution of 2-[1-(3-aminobenzyl)-3-piperidyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (0.339 g, 0.890 mmol) in pyridine (5 ml) was added acetic anhydride (0.101 ml, 1.07 mmol) at 0 °C, and the mixture was stirred for 1 h at room temperature. The mixture was concentrated *in vacuo* and the residue was partitioned between $CHCl_3$ (15 ml×2) and 0.2 N aqueous NaOH (40 ml). The combined $CHCl_3$ layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography ($CHCl_3$/MeOH=24/1, v/v) to give 2-{[3-(6,7-dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)-1-piperidyl]methyl}acetanilide (0.526 g, quantitative) as a yellow syrup. This compound was converted to corresponding oxalate to give **13a** (0.357 g, 67%) as a yellow amorphous powder. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.55—1.61 (2H, m), 1.83—1.86 (1H, m), 2.07 (3H, s), 2.07—2.16 (2H, m), 2.41 (1H, t, J=10.4 Hz), 2.77—2.79 (1H, m), 2.91 (2H, br s), 3.16 (1H, d, J=10.4 Hz), 3.32 (3H, br s), 3.71 (2H, br s), 3.71 (3H, s), 3.72 (3H, s), 4.16 (2H, s), 6.71 (1H, s), 6.77 (1H, s), 7.10 (1H, t, J=7.6 Hz), 7.27—7.32 (2H, m), 7.79 (1H, d, J=7.6 Hz). FAB-MS m/z: 424 (M^++1). *Anal.* Calcd for $C_{25}H_{33}N_3O_3\cdot 2(CO_2H)_2\cdot 0.2H_2O$: C, 57.36; H, 6.21; N, 6.92. Found: C, 57.18; H, 6.39; N, 7.27.

2-{[3-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)piperidino]-methyl}methanesulfonanilide Monooxalate (13a) The title compound was prepared in the same manner as described for **13a** using methanesulfonyl chloride instead of acetic anhydride, in 49% yield. mp 215—216 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.52 (2H, br s), 1.84 (1H, br s), 2.04—2.10 (2H, m), 2.32 (1H, t, J=10.8 Hz), 2.86 (2H, br s), 3.07 (3H, s), 3.07—3.11 (2H, m), 3.20 (2H, br s), 3.70 (3H, s), 3.71 (3H, s), 3.71—3.81 (2H, m), 4.06 (2H, s), 6.69 (1H, s), 6.74 (1H, s), 7.14 (1H, dt, J=8.0, 1.6 Hz), 7.31—7.34 (2H, m), 7.37—7.39 (1H, m). FAB-MS m/z: 460 (M^++1). *Anal.* Calcd for $C_{24}H_{33}N_3O_4S\cdot(CO_2H)_2\cdot 0.3H_2O$: C, 56.26; H, 6.46; N, 7.57; S, 5.78. Found: C, 56.23; H, 6.23; N, 7.52; S, .94.

2-{1-[(1-*tert*-Butoxycarbonyl-4-piperidyl)methyl]-3-piperidyl}-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (16) The title compound was prepared in the same manner as described for **6a** using 1-*tert*-butoxycarbonyl-4-piperidylcarboxyaldehyde (**15**) instead of **5a**. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.02—1.10 (2H, m), 1.22—1.34 (1H, m), 1.45 (9H, s), 1.52—1.99 (8H, m), 2.13—2.22 (2H, m), 2.66—2.71 (2H, m), 2.80—2.86 (6H, m), 3.04—3.06 (1H, m), 3.69—3.78 (2H, m), 3.83 (3H, s), 3.83 (3H, s), 4.07 (2H, br s), 6.51 (1H, s), 6.58 (1H, s). FAB-MS m/z: 474 (M^++1).

6,7-Dimethoxy-2-[1-(4-piperidylmethyl)-3-piperidyl]-1,2,3,4-tetrahydroisoquinoline Trihydrochloride (17) The title compound was prepared in the same manner as described for **10**, in 80% yield. mp 209—213 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.44—1.50 (2H, m), 1.83 (1H, br s), 2.02—2.05 (4H, m), 2.25—2.33 (2H, m), 2.82—3.08 (13H, m), 3.73 (3H, s), 3.74 (3H, s), 4.07 (2H, br s), 4.27—4.44 (2H, m), 6.79 (1H, s), 6.82 (1H, s), 9.09—9.19 (2H, m), 11.43—12.11 (2H, m). FAB-MS m/z: 374 (M^++1). *Anal.* Calcd for $C_{22}H_{35}N_3O_2\cdot 3HCl\cdot 1.4H_2O$: C, 52.00; H, 8.09; N, 8.27; Cl, 20.93. Found: C, 52.17; H, 8.64; N, 8.11; Cl, 20.44.

2-{1-[(1-Acetyl-4-piperidyl)methyl]-3-piperidyl}-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline Dioxalate (18) The title compound was prepared in the same manner as described for **13a**, in 36% yield. mp 115—119 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 0.90—1.11 (2H, m), 1.53—1.77 (4H, m), 1.82—2.01 (3H, m), 1.98 (3H, s), 2.39 (1H, t, J=11.2 Hz), 2.55—2.60 (4H, m), 2.86 (2H, t, J=5.6 Hz), 2.98—3.07 (2H, m), 3.16—3.19 (3H, m), 3.32 (1H, d, J=10.8 Hz), 3.71 (3H, s), 3.72 (3H, s), 3.78 (1H, d, J=12.8 Hz), 4.03 (2H, s), 4.33 (1H, d, J=12.8 Hz), 6.71 (1H, s), 6.74 (1H, s). FAB-MS m/z: 415 (M^++1). *Anal.* Calcd for $C_{24}H_{37}N_3O_3\cdot 2(CO_2H)_2\cdot 1.7H_2O$: C, 53.70; H, 7.15; N, 6.71. Found: C, 53.78; H, 7.36; N, 6.77.

Pharmacology *in Vitro* Tests Male guinea pigs weighting 250—400 g were killed by a blow on the neck, the heart was rapidly removed. Right atria was dissected and mounted vertically in a 30 ml organ bath containing Krebs–Henseleit solution (118.4 mM NaCl, 4.7 mM KCl, 2.5 mM $CaCl_2\cdot 2H_2O$, 1.2 mM KH_2PO_4, 25.0 mM $NaHCO_3$, 1.2 mM $MgSO_4\cdot 7H_2O$, 11.1 mM glucose) at 37 °C and babbled with 95% O_2 and 5% CO_2. The resting tension on the muscle was about 1 g and kept constant through the experiments. Under the condition, the right atria allowed to equilibrate for 90 min with exchange of bath solution every 15 min before drug administration. Amplitude of constriction were measured isometrically by a force-displacement transducer (SB-1T, Nihon Kohden, Tokyo Japan) to obtain spontaneous rates of beating with tachometer (AT-600G, Nihon Kohden, Tokyo Japan) that was triggered by the contractile pulse. After initial spontaneous rate of beating was recorded, a drug dissolved in distilled water and diluted with the experimental Krebs–Henseleit solution to the desired concentration was added to the bath solution cumulatively at 30 min intervals and a concentration–response curve was constructed. A EC_{30} value that mean the concentration of the compounds producing a 30% reduction from initial spontaneous rate of beating, was determined by linear regression.

***In Vivo* Tests** Male Wister rats (270—350 g) were anesthetized with urethane (1.0 g/kg i.p.). The body temperature was kept constant at 37 °C. The femoral vein was cannulated for intravenous administration of drugs. The common carotid artery were cannulated for the recording of systemic blood pressure. Blood pressure was recorded through the cannula connected to a pressure transducer (AP-200T, Nihon Kohden, Tokyo, Japan) and a pressure amplifier (AP-621G, Nihon Kohden, Tokyo, Japan). Heart rate was measured with tachometer (AT-600G, Nihon Kohden, Tokyo, Japan) triggered by the pulsewave of blood pressure. The doses of each compound required to produce a 30% decrease of basal values of heart rate were expressed as ED_{30} values. To obtain a ED_{30} value, tested compounds (0.3—10.0 mg/kg) were administered intravenously in an increasing fashion at 30 min intervals after the stabilization of heart rate and a dose–response curve was constructed. When the time course of effects of compounds on heart rate and mean blood pressure was evaluated, a compound was administered intravenously with single doses after 30 min stabilizing period, and changes in heart rate and blood pressure were observed for 60 min after the administration.

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