Synthesis and Pharmacological Evaluation of 1-Oxo-2-(3-piperidyl)-1,2,3,4-tetrahydroisoquinolines and Related Analogues as a New Class of Specific Bradycardic Agents Possessing I_f Channel Inhibitory Activity

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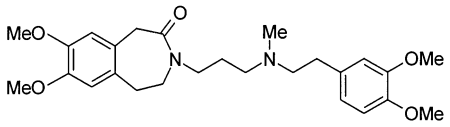
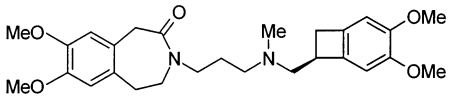
A series of 1-oxo-2-(3-piperidyl)-1,2,3,4-tetrahydroisoquinolines and related analogues were prepared and evaluated for their bradycardic activities in isolated right atrium and in anesthetized rats. (±)-6,7-Dimethoxy-2-{1-[3-(3,4-methylenedioxyphenoxy)propyl]-3-piperidyl}-1,2,3,4-tetrahydroisoquinoline (**4**) was chosen as a lead, and structural modifications were performed on the tetrahydroisoquinoline ring and the terminal aromatic ring. The modifications on the tetrahydroisoquinoline ring revealed that the 1-oxo-1,2,3,4-tetrahydroisoquinoline ring system was optimum structure for both in vitro potency and in vivo efficacy. Furthermore, methoxy, ethoxy, and methoxycarbonyl groups were identified as preferable substituents on the terminal aromatic ring. One of the 1-oxo-1,2,3,4-tetrahydroisoquinoline derivatives, (*R*)-**10a**, was further evaluated for its bradycardic activity and inhibitory activity against I_f currents. Compound (*R*)-**10a** demonstrated potent bradycardic activity in rats with minimal influence on blood pressure after oral administration. The compound also showed inhibition of I_f currents (IC_{50} = 0.32 μM) in guinea pig pacemaker cells.

Introduction

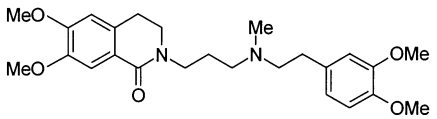
It has been shown that chronically elevated heart rate (HR) raises myocardial oxygen consumption and thereby results in a decline of cardiac energetic efficiency in patients with congestive heart failure, which originates from ischemic heart diseases.[1] Recent studies demonstrated that an increase in HR is one of the major risk factors contributing to cardiovascular morbidity and mortality.[2−5] Therefore, prevention of increased HR is thought to be a desirable therapeutic approach in patients with cardiac diseases. So-called β-blockers and some calcium channel inhibitors are reference drugs for bradycardia, but care must be taken in their use, due to their undesirable effects such as negative inotropic or hypotensive effects.[6,7] These undesirable effects of the above drugs have encouraged the development of another class of bradycardic agents that selectively reduce HR without affecting either strength of heart contraction or blood pressure. This novel class, which have been termed "specific bradycardic agents"[8] includes Zatebradine (UL-FS 49, **1**),[9−11] and Ivabradine (S-16257, **2**),[12−14] for which clinical trials are under way.[15,16] It has recently been revealed that these compounds inhibit one of the most important pacemaker channels, I_f channel, which locate in sinoatrial (SA) node pacemaker cells.[11,13] It is therefore suggested that inhibition of I_f channel may be responsible for the bradycardic effects of specific bradycardic agents.[14]



Zatebradine (**1**)



Ivabradine (**2**)



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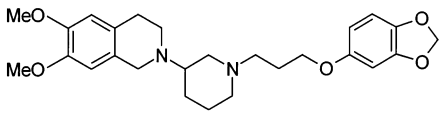

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We found a series of (±)-6,7-dimethoxy-2-(3-piperidyl)-1,2,3,4-tetrahydroisoquinoline derivatives which showed potent bradycardic activities.[17] In particular, a 3-(3,4-methylenedioxyphenoxy)propyl analogue (**4**) demonstrated potent and specific bradycardic activities comparable to those of Zatebradine. In addition, electrophysiological studies in SA node pacemaker cells indicated that compound **4** might act on I_f channel.[17] We chose **4** as a lead for our program to investigate specific bradycardic agents, which focused on enhancement of

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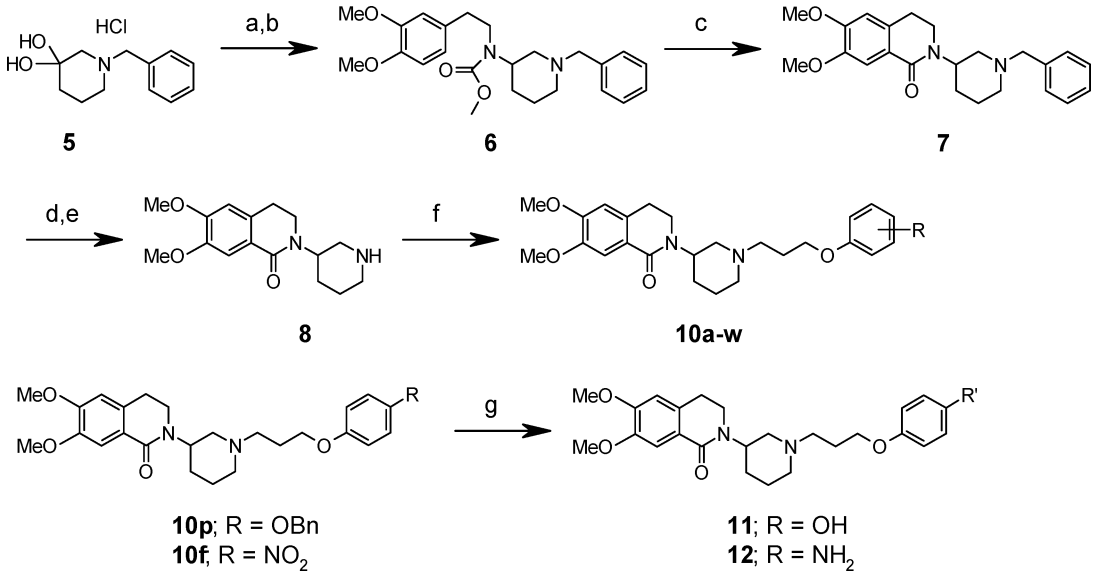
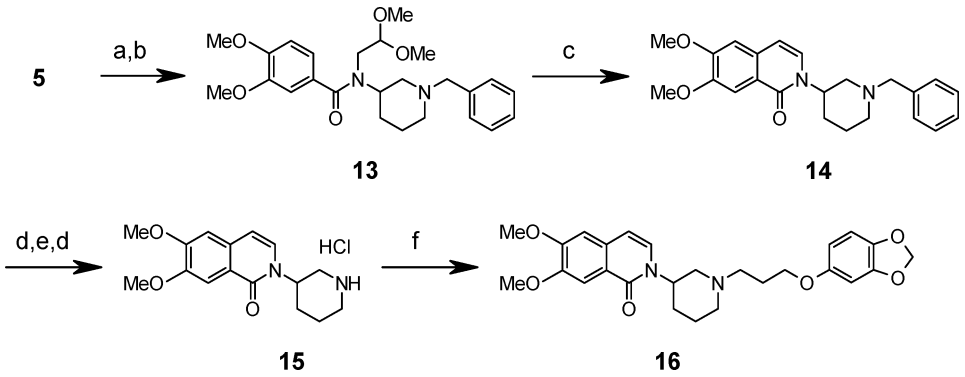
Scheme 1[a]



[a] Conditions: (a) 3,4-dimethoxyphenethylamine, $NaBH(OAc)_3$, AcOH, THF; (b) $ClCO_2Me$, Et_3N, THF; (c) Tf_2O, DMAP, $Cl(CH_2)_2Cl$, 3 days; (d) 4 N HCl (g)/AcOEt; (e) H_2 (3−4 kg/cm^2), 10%Pd/C, AcOH; (f) 3-(aryloxy)propyl bromide (**9a**−**w**), K_2CO_3, CH_3CN, 80 °C; (g) H_2, 10%Pd/C, EtOH.

Scheme 2[a]



[a] Conditions: (a) aminoactaldehyde dimethylacetal, $NaBH(OAc)_3$, AcOH, THF; (b) 3,4-dimethoxybenzoyl chloride, Et_3N, THF; (c) c.HCl, AcOH; (d) 4 N HCl (g)/AcOEt; (e) H_2 (3−4 kg/cm^2), 10% Pd/C, AcOH; (f) 3-(3,4-methylenedioxyphenoxy)propyl bromide (**9a**), K_2CO_3, CH_3CN, 80 °C.

bradycardic activity. The program also aimed at elucidating the effects of the analogues on I_f channel as well as their structure−activity relationships (SAR).

Reiffen and co-workers reported the SAR of Zatebradine and its related analogues which revealed that the benzolactam system played a crucial role in exerting both potent bradycardic activity and selectivity versus blood pressure and cardiac contractility.[10] In addition, a six-membered ring analogue (**3**) showed moderate bradycardic activity without affecting heart contraction or blood pressure.[18] These facts prompted us to apply the benzolactam system to **4**, which gave 1-oxo-1,2,3,4-tetrahydroisoquinoline derivatives. Subsequently, we attempted modifications of the C-3 and C-4 position of the isoquinoline ring. Last, we optimized the substitution pattern of the terminal aromatic ring. All compounds synthesized were evaluated for their bradycardic activities in isolated right atrium (in vitro assay). Compounds with high in vitro activities were studied for their effects on both HR and mean blood pressure (MBP)[19] in rats (in vivo assay). Furthermore, (*R*)-**10a** was examined for its inhibitory activity against I_f currents in SA node pacemaker cells.

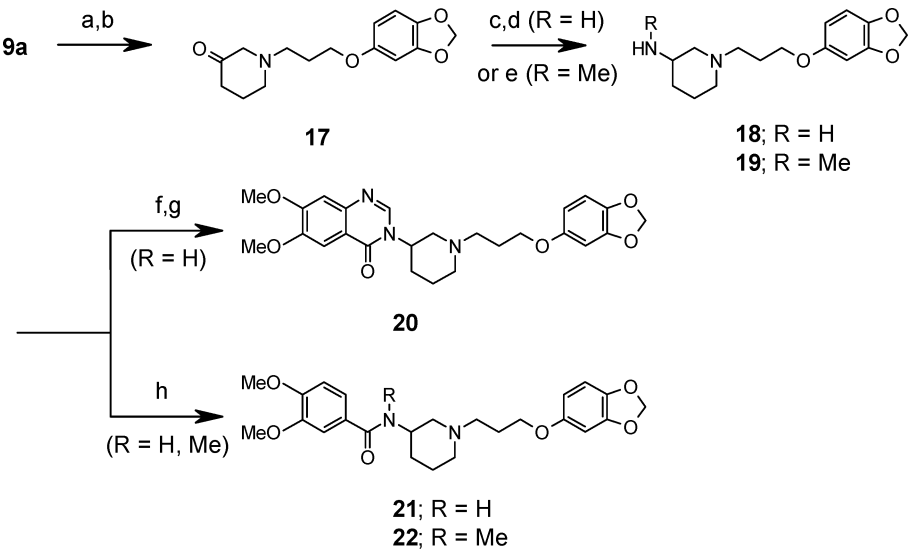
Chemistry

The 1-oxo-1,2,3,4-tetrahydroisoquinoline analogues (**10**) were prepared as shown in Scheme 1. The intermediate amine, **7**, was prepared from the carbamate (**6**) by the cyclization conditions reported by Banwell et al.[20] Subsequent debenzylation followed by N-alkylation with corresponding 3-(aryloxy)propyl bromides (**9a**−**w**) afforded the desired products, **10a**−**w**. Compounds **10p** and **10f** were hydrogenated to give **11** and **12**, respectively.

Scheme 2 shows the preparation of the 1,2-dihydro-1-oxoisoquinoline analogue (**16**). The dimethylacetal, **13**, was cyclized under an acidic condition to give **14**. Subsequent debenzylation and N-alkylation with bromide (**9a**) afforded **16**.

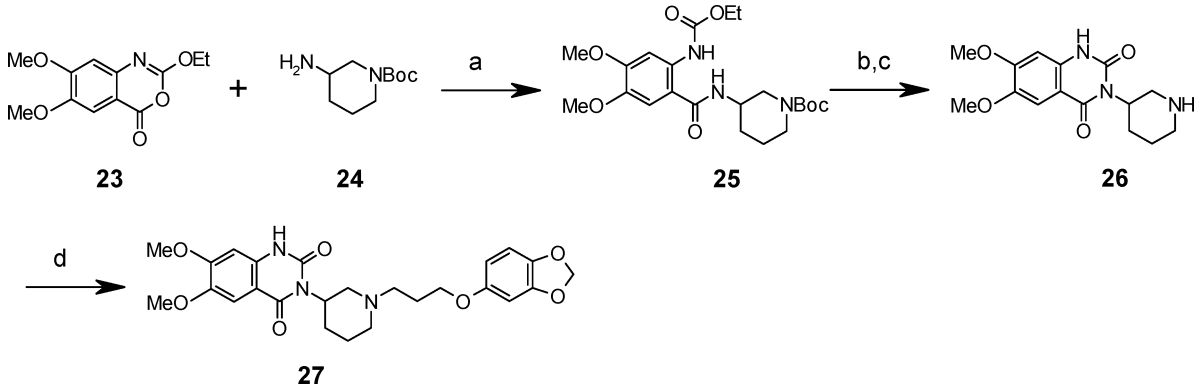
The preparations of the 3,4-dihydro-4-oxoquinazoline analogue (**20**) and benzamide analogues, **21** and **22**, were carried out as shown in Scheme 3. The piperidone (**17**) was reacted with hydroxylamine followed by reduction to give the primary amine, **18**. The secondary amine (**19**) was prepared from **17** by reductive alkylation. Compound **18** was condensed with anthranilic acid and

Scheme 3[a]



[a] Conditions: (a) 3-hydroxypiperidine, K_2CO_3, CH_3CN, 80 °C; (b) $(COCl)_2$, DMSO, Et_3N, CH_2CL_2, −70 °C to 0 °C; (c) *O*-benzylhydroxyamine, pyridine; (d) $LiAlH_4$, THF, reflux; (e) 40% $MeNH_2$/MeOH, $NaBH(OAc)_3$, AcOH, THF; (f) 4,5-dimethoxyanthranilic acid, EDC·HCl, HOBt, $Cl(CH_2)_2Cl$; (g) $HC(OEt)_3$, 150 °C; (h) 3,4-dimethoxybenzoyl chloride, AcOEt.

Scheme 4[a]



[a] Conditions: (a) pyridine, reflux; (b) NaH, DMF, 50 °C; (c) 4 N HCl (g)/AcOEt, MeOH; (d) **9a**, K_2CO_3, CH_3CN, 80 °C.

then cyclized with triethyl orthoformate to give **20**. Alternatively, benzoylation of **18** and **19** yielded benzamide analogues, **21** and **22**, respectively.

For the 2,4-dioxo-1,2,3,4-tetrahydroquinazoline analogue, **27** (Scheme 4), aminopiperidine (**24**)[21] was reacted with 2-ethoxy-4-oxo-1,3-benzoxazin (**23**), which was obtained from the corresponding anthranilic acid,[22] to give **25**. Compound **25** was cyclized using NaH and deprotected to afford the 2,4-dioxo-1,2,3,4-tetrahydroquinazoline analogue (**26**). Finally, compound **26** was converted to **27** by a similar procedure to that described above.

The enantiomers of **10a** were prepared respectively from the enantiomers of **8**, which were obtained using a conventional resolution technique. The absolute configuration of the enantiomers was determined by X-ray crystallographic analysis using (*R*)-**10a**.[23]

Pharmacology

In Vitro Assays. The compounds synthesized were tested for their bradycardic activities in the right atrium isolated from guinea pigs. The EC_{30} value means the concentration of the compound producing a 30% reduction from the initial spontaneous beat rates.

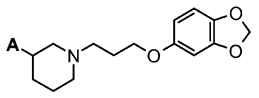
In Vivo Assays. The compounds with high in vitro activities were examined for their effects on both HR and MBP by intravenous (iv) administration of 3 mg/kg in urethane-anesthetized rats. The effect was expressed as a maximal percent change from the initial value. Compound (*R*)-**10a** was further evaluated for its effect on both HR and MBP by oral (po) administration of 10 mg/kg in conscious rats.

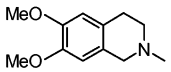
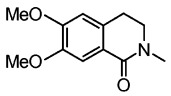
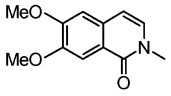
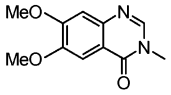
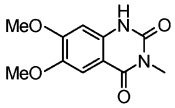
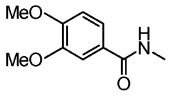
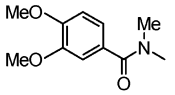
Inhibitory Effect on I_f Currents. Compound (*R*)-**10a** was tested for its inhibitory effect on I_f currents in SA node pacemaker cells isolated from guinea pigs.

Results and Discussion

The structure of the novel compounds and their bradycardic activities in vitro and in vivo are summarized in Tables 1 and 2. Initially, modifications of the 1,2,3,4-tetrahydroisoquinoline ring were attempted (Table 1). Introduction of an oxo moiety at the isoquinoline C-1 of **4** (**10a**) resulted in a 4-fold increase of in vitro potency (EC_{30} = 0.067 μM). In vivo tests showed that compound **10a** had potent bradycardic activity with a slight influence on MBP. The 1,2-dihydro analogue (**16**) was less potent than **10a**, particularly in vivo. It is interesting to note that compound **16** showed weak

Table 1. Effect of Modifications of the 1,2,3,4-Tetrahydroisoquinoline Ring



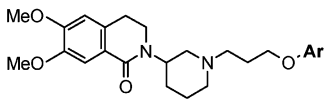
compd	A	Right atrium EC_{30},[a] μM	Anesthetized rats %change[b] at 3 mg/kg iv[c] HR	MBP	mp, C (solvent[d])	formula	anal.
4		0.25±0.03	–47±5	–7.1±5	167–169 (N)	$C_{26}H_{34}N_2O_5 \cdot 2HCl \cdot 0.5H_2O$	C,H,N,Cl
10a		0.067±0.003	–48±5	–14±4	212–217 (A–N)	$C_{26}H_{32}N_2O_6 \cdot HCl$	C,H,N,Cl
16		0.20±0.04	–26[e]	11[e]	205–208 (A–N)	$C_{26}H_{30}N_2O_6 \cdot HCl$	C,H,N,Cl
20		0.26±0.03	–34±2	–20±5	142–146 (E)	$C_{25}H_{29}N_3O_6 \cdot HCl \cdot 1.2H_2O$	C,H,N,Cl
27		0.92±0.1	N.T.[f]	N.T.[f]	227–233 (N–M)	$C_{25}H_{29}N_3O_7 \cdot HCl \cdot 0.4H_2O$	C,H,N,Cl
21		0.42±0.07	–29±3	–11±2	165–167 (E–T)	$C_{24}H_{30}N_2O_6 \cdot HCl$	C,H,N,Cl
22		3.5±0.9	N.T.[f]	N.T.[f]	178–181 (E)	$C_{25}H_{32}N_2O_6 \cdot HCl$	C,H,N,Cl
Zatebradine		0.26±0.05	–47±3	5.4±3			

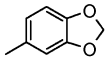
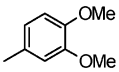
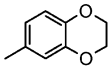
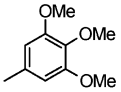
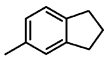
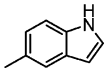
[a] The concentration required to produce a 30% reduction from the initial spontaneous beat rates in right atrium of guinea pigs. Each value indicates a mean ± SEM from three to six experiments. [b] Percent change from the initial value in rats as mean ± SEM from three to four experiments. [c] The doses are in terms of the salt form. [d] Recrystallization solvents: A, AcOEt; N, CH_3CN; E, EtOH; M, MeOH; T, Et_2O. [e] Mean from two experiments. [f] Not tested.

hypertensive activity (11% increase). The 3,4-dihydro-4-oxoquinazoline analogue (**20**) had less potency than **10a**. In addition, compound **20** seemed to have a certain hypotensive effect despite its weaker bradycardic activity. The 2,4-dioxo-1,2,3,4-tetrahydroquinazoline analogue (**27**) was an even weaker agent. The ring-opening analogues (benzamide analogues), **21** and **22**, showed considerably weak activities in comparison to **10a** (EC_{30} = 0.42 μM and 3.5 μM, respectively). These results allowed us to conclude that the 1-oxo-1,2,3,4-tetrahydroisoquinoline ring system was optimum for this part of the structure. The results also demonstrated that modifications on the isoquinoline C-3 and C-4 positions markedly and diversely affected not only the compounds' bradycardic potencies but also their effects on MBP. Despite the similarity in the electronic and steric characteristics of **10a** and **22**, a 50-fold difference between their level of bradycardic activity in vitro was observed. The rigid bicyclic structure of **10a** may contribute to the enhancement of in vitro activity by keeping the molecule in a desirable conformation. Thus we chose **10a** as a new lead and proceeded to make further modifications on the terminal aromatic ring (Table 2).

Substitution for the 3,4-methylenedioxy moiety of **10a** by hydrogens (**10b**) caused a 6-fold decrease of in vitro activity. Among the monosubstituted analogues (**10c**−**e**), the 4-methoxy analogue (**10e**) showed the highest level of in vitro activity (EC_{30} = 0.099 μM). Moreover, compound **10e** had an equal in vivo potency to that of **10a**. These results suggested that the substituent at the 4-position was important in both in vitro and in vivo activity. We then examined the effects of substituents at the 4-position in terms of electronic, steric, and hydrophobic properties. Compounds with an electron-withdrawing group (**10f**−**k**) showed between 1/4 and 1/10 activity of **10a**. Among them, the nitro analogue (**10f**) alone exhibited striking hypertensive activity (41% increase) without bradycardic activity. The ethoxy analogue (**10m**) showed potent in vitro and in vivo activity, being comparable to those of the methoxy analogue (**10e**). However, the bulkier the ethereal alkyl groups from **10m**, the weaker in vitro potencies by the analogues (**10n**−**p**). Compounds with hydrophilic substituents, namely the acetamide (**10q**), hydroxy (**11**), and amino (**12**) analogues had 1/10 or less of the level of in vitro activity of **10a**. It was noteworthy that the methoxycarbonyl analogue (**10r**) showed potent activity (EC_{30} = 0.11 μM), whereas the carboxamide analogue (**10s**) had considerably weaker potency (EC_{30} = 5.7 μM), despite no significant differences between these compounds with respect to electronic and steric

Table 2. Effect of Modifications of the Terminal Aromatic Ring



compd	Ar	Right atrium EC_{30},[a] μM	Anesthetized rats %change[b] at 3 mg/kg iv[c] HR	MBP	mp, C (solvent[d])	formula	anal.
10a		0.067±0.003	–48±5	–14±4	212–217 (A–N)	$C_{26}H_{32}N_2O_6$ ·HCl	C,H,N,Cl
10b	C_6H_5	0.39±0.03	–32±4	3.2±2	190–205 (A–E)	$C_{25}H_{32}N_2O_4$ ·HCl·0.2H_2O	C,H,N,Cl
10c	2-C_6H_4OMe	0.39±0.04	N.T.[e]	N.T.[e]	195–199 (A–N)	$C_{26}H_{34}N_2O_5$ ·HCl·0.5H_2O	C,H,N,Cl
10d	3-C_6H_4OMe	0.14±0.02	–47[f]	–11[f]	189–194 (A–N)	$C_{26}H_{34}N_2O_5$ ·HCl	C,H,N,Cl
10e	4-C_6H_4OMe	0.099±0.02	–49±3	–16±4	199–207 (A–N)	$C_{26}H_{34}N_2O_5$ ·HCl	C,H,N,Cl
10f	4-$C_6H_4NO_2$	0.27±0.04	–5.6±0.6	41±7	221–229 (A–E)	$C_{25}H_{31}N_3O_6$ ·HCl	C,H,N,Cl
10g	4-C_6H_4CN	0.24±0.03	–23±2	–6.8±9	207–212 (A–N)	$C_{26}H_{31}N_3O_4$ ·HCl	C,H,N,Cl
10h	4-$C_6H_4CF_3$	0.79±0.4	N.T.[e]	N.T.[e]	217–231 (A–E)	$C_{26}H_{31}N_2O_4F_3$ ·HCl	C,H,N,Cl,F
10i	4-C_6H_4F	0.24±0.08	–39±2	–17±2	187–192 (N)	$C_{25}H_{31}N_2O_4F$ ·HCl·0.2H_2O	C,H,N,Cl,F
10j	4-C_6H_4Cl	0.35±0.06	–32±3	–12±5	205–211 (A)	$C_{25}H_{31}N_2O_4Cl$ ·HCl	C,H,N,Cl
10k	4-C_6H_4Br	0.47±0.08	N.T.[e]	N.T.[e]	214–218 (A–N)	$C_{25}H_{31}N_2O_4Br$ ·HCl	C,H,N,Br,Cl
10l	4-C_6H_4Me	0.14±0.02	–37[f]	–12[f]	205–209 (A–N)	$C_{26}H_{34}N_2O_4$ ·HCl·0.2H_2O	C,H,N,Cl
10m	4-C_6H_4OEt	0.097±0.01	–49[f]	–7.8[f]	208–213 (A–N)	$C_{27}H_{36}N_2O_5$ ·HCl	C,H,N,Cl
10n	4-C_6H_4O*n*-Pr	0.27±0.03	N.T.[e]	N.T.[e]	178–185 (A–E)	$C_{28}H_{38}N_2O_5$ ·HCl·0.1H_2O	C,H,N,Cl
10o	4-C_6H_4O*i*-Pr	0.33±0.1	N.T.[e]	N.T.[e]	189–196 (A–E)	$C_{28}H_{38}N_2O_5$ ·HCl	C,H,N,Cl
10p	4-C_6H_4OBn	1.3±0.3	N.T.[e]	N.T.[e]	187–192 (A–N)	$C_{32}H_{38}N_2O_5$ ·HCl	C,H,N,Cl
10q	4-C_6H_4NHCOMe	0.76±0.18	N.T.[e]	N.T.[e]	220–232 (A–E)	$C_{27}H_{35}N_3O_5$ ·HCl	C,H,N,Cl
11	4-C_6H_4OH	0.89±0.09	N.T.[e]	N.T.[e]	215–220 (I–M)	$C_{25}H_{32}N_2O_5$ ·HCl·0.6H_2O	C,H,N,Cl[g]
12	4-$C_6H_4NH_2$	1.6±0.09	N.T.[e]	N.T.[e]	223–231 (A–E)	$C_{25}H_{33}N_3O_4$ ·HCl	C,H,N,Cl
10r	4-$C_6H_4CO_2$Me	0.11±0.02	–30[f]	–2.3[f]	202–207 (A–N)	$C_{27}H_{34}N_2O_6$ ·HCl	C,H,N,Cl
10s	4-$C_6H_4CONH_2$	5.7±0.5	N.T.[e]	N.T.[e]	208–214 (A–N)	$C_{26}H_{33}N_3O_5$ ·HCl·0.6H_2O	C,H,N,Cl
10t		0.11±0.01	–56±0.3	–18±2	196–203 (A–N)	$C_{27}H_{36}N_2O_6$ ·HCl	C,H,N,Cl
10u		0.13±0.01	–44[f]	–12[f]	208–214 (P)	$C_{27}H_{34}N_2O_6$ ·HCl	C,H,N,Cl
10v		1.6±0.3	N.T.[e]	N.T.[e]	108–111 (A–N)	$C_{28}H_{38}N_2O_7$ ·HCl·0.3H_2O	C,H,N,Cl
10w		0.89±0.1	N.T.[e]	N.T.[e]	210–219 (A–N)	$C_{28}H_{36}N_2O_4$ ·HCl	C,H,N,Cl
10x		0.36±0.02	N.T.[e]	N.T.[e]	195–199 (A–M)	$C_{27}H_{33}N_3O_4$ ·HCl·0.8H_2O	C,H,N,Cl

[a–c] See the corresponding footnotes of Table 1. [d] Recrystallization solvents: A, AcOEt; N, CH_3CN; E, EtOH; M, MeOH; I, *i*-PrOH; P, *n*-PrOH. [e] Not tested. [f] Mean from two experiments. [g] Calcd 7.27; found 6.82.

Table 3. Enantiomers of Compound **10a**

compd	right atrium EC_{30},[a] μM	anesthetized rats % change[b] at 3 mg/kg iv[c] HR	MBP	mp, C (solvent[d])	formula	anal.
10a	0.067 ± 0.003	−48 ± 5	−14 ± 4	212−217 (A−N)	$C_{26}H_{32}N_2O_6$·HCl	C,H,N,Cl
(*S*)-**10a**	0.068 ± 0.005	−53 ± 3	−23 ± 2	200−202 (E)	$C_{26}H_{32}N_2O_6$·HCl	C,H,N,Cl
(*R*)-**10a**	0.079 ± 0.007	−55 ± 2	−13 ± 2	190−194 (E)	$C_{26}H_{32}N_2O_6$·HCl·0.2H_2O	C,H,N,Cl

[a−c] See the corresponding footnotes of Table 1. [d] Recrystallization solvents: A, AcOEt; N, CH_3CN; E, EtOH.

properties. Based on these results, we performed correlation analyses using substituent parameters. We plotted pEC_{30} (−log EC_{30}) against three substituent parameters; π (hydrophobicity), σ_p (electronic property), and MR (steric bulk)[24] (Figure 1). As shown in the Panel A, a characteristic reversed U-shape correlation was observed in the $pEC_{30} - \pi$ plot, with a summit around $\pi = 0$. In contrast, there seemed to be no correlation between pEC_{30} versus σ_p or MR (Panels B, C). It was assumed that appropriate hydrophobicity (around $\pi = 0$) at the 4-position was important to exert potent in vitro activity (e.g., methoxy, ethoxy, methoxycarbonyl). We made further modifications on the terminal aromatic ring. The 3,4-dimethoxy (**10t**) and 3,4-ethylenedioxy (**10v**) analogues showed potent in vitro and in vivo activities. However, the 3,4,5-trimethoxy analogue (**10t**) was a considerably weaker agent. There may be a limited bulk-tolerance in this region. Substitution for two oxygens of **10a** by methylenes gave the indane analogue (**10w**), which showed 13-fold less potent in vitro activity of **10a**. The oxygen atoms on the aromatic ring of **10a** may contribute to the potent in vitro activity by producing the appropriate hydrophobicity of the molecule, or by interacting directly with the active sites. The contribution of the oxygen atoms was also supported by the lower activity observed for the indole analogue (**10x**).

Last, the enantiomers of **10a** were evaluated (Table 3). There was no significant difference in both in vitro activity and the effect on HR between the enantiomers. However, it was clear that (*R*)-**10a** had a lesser effect on MBP (13% decrease) than (*S*)-**10a** did (23% decrease). Consequently, we recognized (*R*)-**10a** as an excellent "specific bradycardic agent".

On the basis of in vitro and in vivo assay results, (*R*)-**10a** was submitted to a further pharmacological evaluation. Compound (*R*)-**10a** (10 mg/kg, the salt form) was orally administered to conscious rats and HR and MBP were monitored (Figure 2). Compound (*R*)-**10a** reduced spontaneous HR up to a 29% decrease with minimal influence on MBP. Moreover, its bradycardic effect was long-lasting (over 8 h).

The HR is regulated by an electrical impulse that originates in SA node pacemaker cells. In these cells, I_f channel is hypothesized to be responsible for the rate of Phase 4 slow depolarization, which affects the impulse frequency:[25,26] That is, activation of I_f channel leads to an increase in the impulse frequency (= HR) through an increase of the rate of Phase 4 slow depolarization. Thus we examined the effect of (*R*)-**10a** on I_f currents in SA node pacemaker cells using whole-cell patch configuration. Compound (*R*)-**10a** inhibited I_f currents concentration-dependently with an IC_{50} value of 0.32 μM (Figure 3), suggesting that the potent bradycardic effect of (*R*)-**10a** was associated with direct inhibition of I_f channel in SA node pacemaker cells.

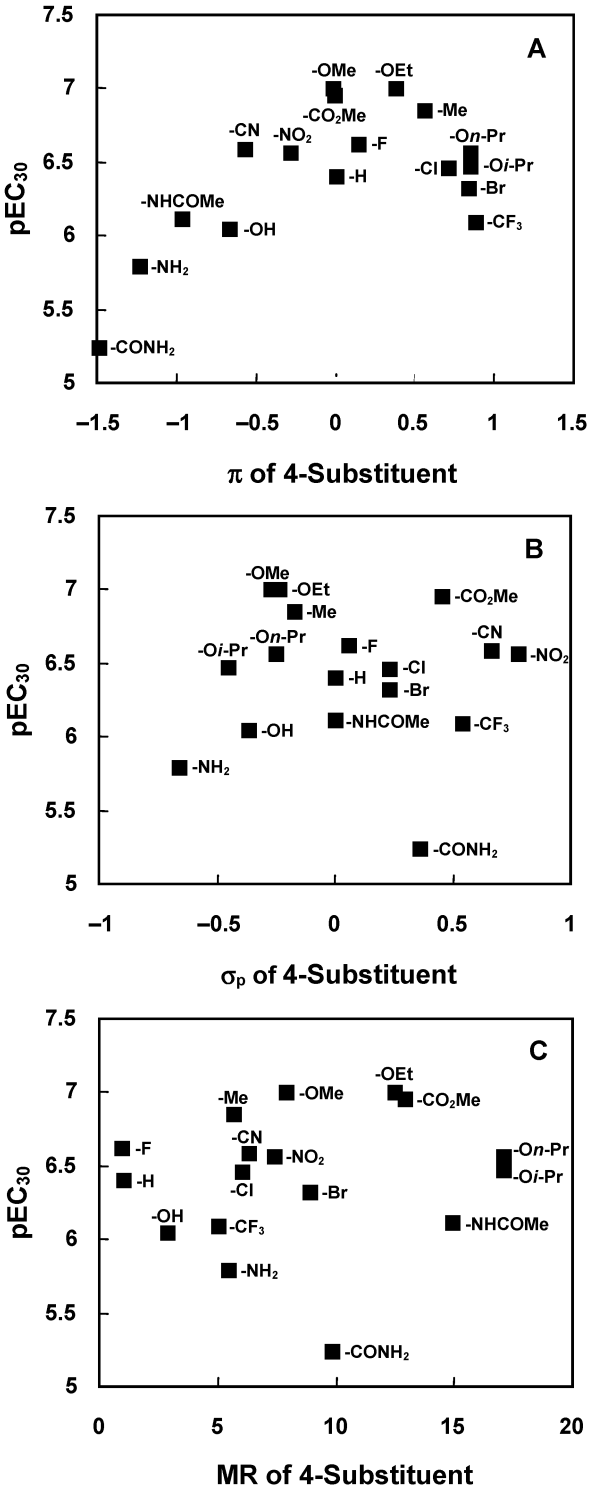


Figure 1. Plot of pEC_{30} against π, σ_p, and MR of 4-substituent, for **10b**, **10e**−**o**, **10q**−**s**, **11**, and **12**.

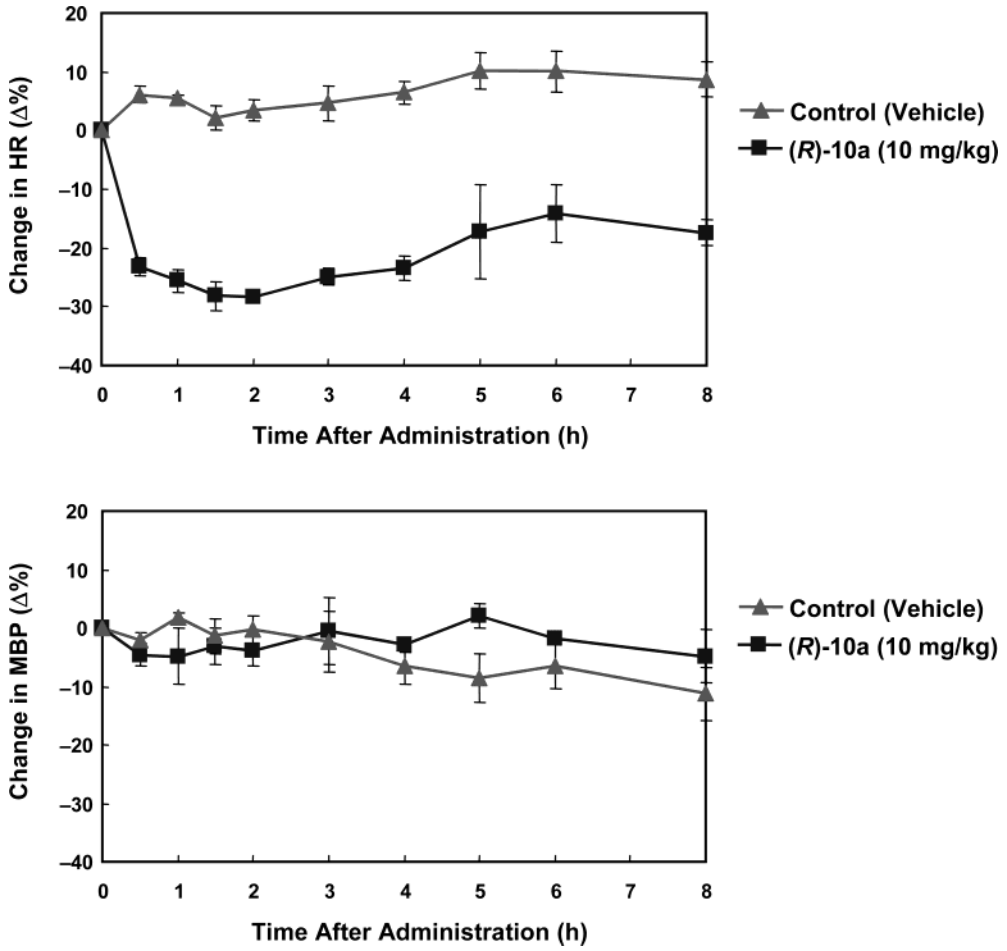


Figure 2. Effects of (*R*)-**10a** on heart rate and mean blood pressure in conscious rats. Compound (*R*)-**10a** (10 mg/kg, the salt form) was orally administered at time 0. The values are mean ± SEM from four experiments.

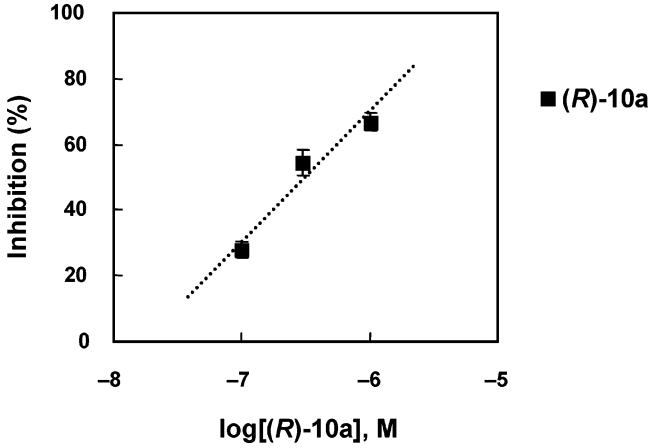


Figure 3. Effects of (*R*)-**10a** on I_f currents. Each point represents mean ± SEM from four experiments. The line represents the linear regression.

Conclusion

A series of 1-oxo-2-(3-piperidyl)-1,2,3,4-tetrahydroisoquinolines and related analogues, which were derived from **4**, have been described as bradycardic agents. Introduction of an oxo moiety at the isoquinoline C-1 position gave the compound **10a**, which had a 4-fold higher in vitro potency. Modifications of the C-3 and C-4 positions of the tetrahydroisoquinoline ring markedly and diversely affected not only the compounds' bradycardic potencies but also their effects on MBP. Modifications of the terminal aromatic ring revealed that appropriate hydrophobicity (around $\pi = 0$) at the 4-position was important to exert potent in vitro activity (e.g., methoxy, ethoxy, methoxycarbonyl). At the same time, it was found that the oxygen atoms on the aromatic ring contribute to the potent in vitro activity. The optical resolution of **10a** led to the finding that (*R*)-**10a** was an excellent "specific bradycardic agent." On the basis of pharmacodynamic observation, it appears that (*R*)-**10a** was orally absorbed and its bradycardic effect was long-lasting. In electrophysiological studies, (*R*)-**10a** was found to inhibit I_f currents with an IC_{50} value of 0.32 μM. The inhibition of I_f currents by (*R*)-**10a** strongly suggested implication of I_f channel in the potent bradycardic activity of the compound. This study could provide a novel approach to I_f channel inhibitors with potent bradycardic activities.

Experimental Section

Chemistry. Melting points were determined with a Yanaco MP-500D melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a JEOL JNM-LA300 or a JEOL JNM-EX400 spectrometer and the chemical shifts are expressed in δ (ppm) values with tetramethylsilane as an internal standard (in NMR description, s = singlet, d = doublet, t = triplet, m = multiplet, and br = broad peak). Mass spectra were recorded on a JEOL JMS-LX2000 spectrometer. For salts, assignments of ion peaks are based on the basic component. The elemental analyses were performed with a Yanaco MT-5 microanalyzer (C, H, N) and a Yokogawa IC-7000S ion chromatographic analyzer (halogens) and were

within ±0.4% of theoretical values, unless otherwise stated. The optical purity of optically active compounds were examined by analytical chiral column (Daicel CHIRALPAK AD, i.d. = 0.46 cm, *l* = 25 cm). The HPLC condition was as follows: mobile phase, *i*-PrOH/hexane/Et_2NH = 500/500/1; flow rate, 0.5 mL/min; detection wavelength, 254 nm. Optical rotation measurements were obtained with a Horiba SEPA-200 polarimeter. Drying of organic solutions during workup was done over anhydrous Na_2SO_4.

Methyl (±)-*N*-(1-Benzyl-3-piperidyl)-*N′*-(3,4-dimethoxyphenethyl)carbamate (6). To a suspension of 1-benzyl-3-piperidone monohydrochloride monohydrate **5** (10.0 g, 44.3 mmol) and 3,4-dimethoxyphenethylamine (8.03 g, 44.3 mmol) in THF (100 mL) were added AcOH (2.54 mL, 44.3 mmol) and $NaBH(OAc)_3$ (10.3 g, 48.7 mmol), and the mixture was stirred at room temperature for 1 h. The reaction mixture was made alkaline with 5 N NaOH aq at 0 °C, then extracted with $CHCl_3$ (50 mL × 2). The combined extract was dried and concentrated in vacuo to give 1-benzyl-3-[(3,4-dimethoxyphenethyl)amino]-piperidine (14.2 g) as a yellow oil. To a solution of compound obtained above (14.2 g, 40.1 mmol) and Et_3N (6.70 mL, 48.1 mmol) in THF (100 mL) was added dropwise a solution of methyl chloroformate (3.40 mL, 44.1 mmol) in THF (10 mL) at 0 °C, and the mixture was stirred at 0 °C for 1 h. The resulting mixture was concentrated in vacuo, and the residue was dissolved in H_2O (150 mL), then extracted with AcOEt (50 mL × 2). The combined extract was washed with 1 N NaOH aq (100 mL) and was dried and concentrated in vacuo to give **6** (16.2 g, 88% from **5**) as a yellow oil. This material may be used next cyclization step or converted to its oxalate salt. The oxalate salt was obtained from MeOH−AcOEt as a colorless powder: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.68−1.78 (4H, m), 2.41 (2H, br s), 2.66 (2H, br s), 2.95−2.97 (2H, m), 3.27−3.29 (2H, m), 3.60 (3H, s), 3.72 (3H, s), 3.74 (3H, s), 3.95 (3H, br s), 6.70 (1H, d, *J* = 7.2 Hz), 6.78 (1H, s), 6.86 (1H, d, *J* = 7.2 Hz), 7.40 (5H, br s); MS (FAB) *m*/*z* 413 (MH^+).

(±)-2-(1-Benzyl-3-piperidyl)-6,7-dimethoxy-1-oxo-1,2,3,4-tetrahydroisoquinoline (7). To a solution of **6** (6.31 g, 15.3 mmol) and 4-(dimethylamino)pyridine (4.67 g, 38.2 mmol) in CH_2Cl_2 (120 mL) was added dropwise a solution of trifluoromethanesulfonic anhydride (10.3 mL, 61.2 mmol) in CH_2Cl_2 (10 mL) at 0 °C, and the mixture was stirred at room temperature for 3 days. The reaction mixture was partitioned between $CHCl_3$ (50 mL × 2) and H_2O (150 mL), and the $CHCl_3$ layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 49/1) to give **7** (3.11 g, 53%) as a yellow oil. This material may be converted to its hydrochloride salt. The hydrochride salt was obtained from EtOH−AcOEt as a colorless powder: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.74−1.83 (4H, m), 2.87 (2H, br s), 2.88 (1H, br s), 3.19−3.24 (2H, m), 3.31 (1H, br s), 3.44 (2H, br s), 3.75 (3H, s), 3.81 (3H, s), 4.32 (2H, t, *J* = 4.8 Hz), 4.85−4.87 (1H, m), 6.89 (1H, s), 7.34 (1H, s), 7.46−7.48 (3H, m), 7.59−7.61 (2H, m), 10.64 (1H, br s); MS (FAB) *m*/*z* 381 (MH^+).

(±)-6,7-Dimethoxy-1-oxo-2-(3-piperidyl)-1,2,3,4-tetrahydroisoquinoline (8). To a solution of **7** (3.09 g, 8.12 mmol) in AcOEt (40 mL) was added 4 N HCl (g)/AcOEt (2.44 mL, 9.75 mmol), and the mixture was concentrated in vacuo. To a solution of the residual solid in AcOH (20 mL) was added Pd/C (10 w/w %, 339 mg), and the mixture was stirred under hydrogen pressure (3−4 kg/cm^2) at room temperature for 24 h. The catalyst was removed by filtration and the filtrate was concentrated in vacuo. The residue was dissolved in H_2O (20 mL) and made alkaline with 5 N NaOH aq at 0 °C, then extracted with $CHCl_3$ (30 mL × 2). The combined extract was dried and concentrated in vacuo to give **8** (1.86 g, 79%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58−1.73 (2H, m), 1.80−1.90 (2H, m), 2.46−2.53 (1H, m), 2.66−2.72 (1H, m), 2.84−2.87 (2H, m), 3.02−3.09 (2H, m), 3.41−3.53 (2H, m), 3.73 (3H, s), 3.84 (3H, s), 4.59−4.66 (1H, m), 6.63 (1H, s), 7.60 (1H, s); MS (FAB) *m*/*z* 291 (MH^+).

3-(Aryloxy)propyl Bromide 9a−x: General Procedure. The synthesis of 3-(3,4-methylenedioxyphenoxy)propyl bromide (**9a**) is typical. To a solution of sesamol (6.91 g, 50.0 mmol) in CH_3CN (100 mL) were added K_2CO_3 (10.4 g, 75.0 mmol) and 1,3-dibromopropane (25.4 mL, 250 mmol), and the mixture was stirred at 80 °C for 7 h. After being cooled at room temperature, the mixture was concentrated in vacuo. The residue was taken up with $CHCl_3$ (100 mL), and the $CHCl_3$ layer was washed with 0.2 N NaOH aq (100 mL × 2), then dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/AcOEt = 9/1) to give **9a** (9.61 g, 74%) as a colorless solid: ^{1}H NMR (90 MHz, $CDCl_3$) δ 2.14−2.41 (2H, m), 3.59 (2H, t, *J* = 6.4 Hz), 4.03 (2H, t, *J* = 5.9 Hz), 5.91 (2H, s), 6.32 (1H, dd, *J* = 8.4, 2.4 Hz), 6.50 (1H, d, *J* = 2.4 Hz), 6.70 (1H, d, *J* = 8.4 Hz); MS (FAB) *m*/*z* 259 (MH^+), 261 ($MH^+ + 2$).

General Procedure for the Preparation of (±)-2-{1-[3-(Aryloxy)propyl]-3-piperidyl}-6,7- dimethoxy-1-oxo-1,2,3,4-tetrahydroisoquinoline 10a−x. The compounds were prepared by treatment of **8** with **9**.

(±)-6,7-Dimethoxy-2-{1-[3-(3,4-methylenedioxyphenoxy)-propyl]-3-piperidyl}-1-oxo-1,2,3,4-tetrahydroisoquinoline Hydrochloride (10a). To a solution of **8** (581 mg, 2.00 mmol) in CH_3CN (10 mL) were added K_2CO_3 (304 mg, 2.20 mmol) and **9a** (544 mg, 2.10 mmol), and the mixture was stirred at 80 °C for 12 h. After being cooled at room temperature, the mixture was concentrated in vacuo. The residue was partitioned between $CHCl_3$ (30 mL × 2) and H_2O (40 mL), then the $CHCl_3$ layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 49/1) to give the free base of **10a** (962 mg, 100%) as a slightly yellow oil. This material was converted to its hydrochloride salt by treating with 4 N HCl (g)/AcOEt (0.600 mL, 2.40 mmol). The crude salt was recrystallized from AcOEt−CH_3CN to give **10a** (780 mg, 77%) as a colorless powder: mp 212−217 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.74−1.95 (4H, m), 2.15−2.20 (2H, m), 2.86−2.92 (3H, m), 3.16−3.22 (3H, m), 3.39−3.49 (4H, m), 3.77 (3H, s), 3.82 (3H, s), 3.98 (2H, t, *J* = 6.0 Hz), 4.86−4.92 (1H, m), 5.96 (2H, s), 6.38 (1H, dd, *J* = 8.4, 2.2 Hz), 6.64 (1H, d, *J* = 2.0 Hz), 6.82 (1H, d, *J* = 8.8 Hz), 6.90 (1H, s), 7.38 (1H, s), 10.47 (1H, br s); MS (FAB) *m*/*z* 469 (MH^+). Anal. ($C_{26}H_{32}N_2O_6$·HCl) C, H, N, Cl.

(±)-6,7-Dimethoxy-2-[1-(3-phenoxypropyl)-3-piperidyl]-1-oxo-1,2,3,4-tetrahydroisoquinoline Hydrochloride (10b): (84%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.75−1.95 (4H, m), 2.19−2.26 (2H, m), 2.86−2.89 (3H, m), 3.18−3.25 (3H, m), 3.40−3.50 (4H, m), 3.77 (3H, s), 3.82 (3H, s), 4.06 (2H, t, *J* = 6.0 Hz), 4.88−4.93 (1H, m), 6.90 (1H, s), 6.93−6.98 (3H, m), 7.30 (2H, t, *J* = 8.0 Hz), 7.38 (1H, s), 10.65 (1H, br s); MS (FAB) *m*/*z* 425 (MH^+). Anal. ($C_{25}H_{32}N_2O_4$·HCl·0.2H_2O) C, H, N, Cl.

(±)-6,7-Dimethoxy-2-{1-[3-(2-methoxyphenoxy)propyl]-3-piperidyl}-1-oxo-1,2,3,4-tetrahydroisoquinoline Hydrochloride (10c): (69%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.75−1.96 (4H, m), 2.20−2.24 (2H, m), 2.86−2.89 (3H, m), 3.19−3.30 (3H, m), 3.39−3.52 (4H, m), 3.76 (3H, s), 3.77 (3H, s), 3.82 (3H, s), 4.04 (2H, t, *J* = 6.0 Hz), 4.88−4.94 (1H, m), 6.86−6.94 (3H, m), 6.97−6.99 (2H, m), 7.38 (1H, s), 10.53 (1H, br s); MS (FAB) *m*/*z* 455 (MH^+). Anal. ($C_{26}H_{34}N_2O_5$·HCl·0.5H_2O) C, H, N, Cl.

(±)-6,7-Dimethoxy-2-{1-[3-(3-methoxyphenoxy)propyl]-3-piperidyl}-1-oxo-1,2,3,4-tetrahydroisoquinoline Hydrochloride (10d): (16%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.74−2.00 (4H, m), 2.18−2.20 (2H, m), 2.85−2.92 (3H, m), 3.20−3.47 (7H, m), 3.73 (3H, s), 3.77 (3H, s), 3.82 (3H, s), 4.05 (2H, t, *J* = 6.0 Hz), 4.80−4.90 (1H, m), 6.48−6.56 (3H, m), 6.90 (1H, s), 7.16−7.22 (1H, m), 7.38 (1H, s), 10.30 (1H, br s); MS (FAB) *m*/*z* 455 (MH^+). Anal. ($C_{26}H_{34}N_2O_5$·HCl) C, H, N, Cl.

(±)-6,7-Dimethoxy-2-{1-[3-(4-methoxyphenoxy)propyl]-3-piperidyl}-1-oxo-1,2,3,4-tetrahydroisoquinoline Hydrochloride (10e): (80%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.75−1.95 (4H, m), 2.14−2.21 (2H, m), 2.86−2.89 (3H, m), 3.16−3.24 (3H, m), 3.39−3.50 (4H, m), 3.69 (3H, s), 3.77 (3H, s), 3.82 (3H, s), 3.99 (2H, t, *J* = 6.0 Hz), 4.86−4.92 (1H, m), 6.85−6.90

(5H, m), 7.38 (1H, s), 10.45 (1H, br s); MS (FAB) *m/z* 455 (MH^+). Anal. ($C_{26}H_{34}N_2O_5$·HCl) C, H, N, Cl.

(±)-6,7-Dimethoxy-2-{1-[3-(4-nitrophenoxy)propyl]-3-piperidyl}-1-oxo-1,2,3,4-tetrahydroisoquinoline Hydrochloride (10f): (81%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.76−1.96 (4H, m), 2.25−2.28 (2H, m), 2.88 (3H, br s), 3.17−3.30 (3H, m), 3.41−3.51 (4H, m), 3.77 (3H, s), 3.81 (3H, s), 4.24 (2H, t, J = 6.0 Hz), 4.86−4.92 (1H, m), 6.90 (1H, s), 7.17 (2H, d, J = 9.6 Hz), 7.38 (1H, s), 8.23 (2H, d, J = 8.8 Hz), 10.33 (1H, br s); MS (FAB) *m/z* 470 (MH^+). Anal. ($C_{25}H_{31}N_3O_6$·HCl·) C, H, N, Cl.

(±)-2-{1-[3-(4-Cyanophenoxy)propyl]-3-piperidyl}-6,7-dimethoxy-1-oxo-1,2,3,4-tetrahydroisoquinoline Hydrochloride (10g): (72%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.75−1.96 (4H, m), 2.21−2.25 (2H, m), 2.86−2.89 (3H, m), 3.16−3.24 (3H, m), 3.40−3.51 (4H, m), 3.77 (3H, s), 3.81 (3H, s), 4.17 (2H, t, J = 6.0 Hz), 4.88 (1H, br s), 6.90 (1H, s), 7.12 (2H, d, J = 8.8 Hz), 7.38 (1H, s), 7.80 (2H, d, J = 9.6 Hz), 10.38 (1H, br s); MS (FAB) *m/z* 450 (MH^+). Anal. ($C_{26}H_{31}N_3O_4$·HCl) C, H, N, Cl.

(±)-6,7-Dimethoxy-2-{1-[3-(4-trifluoromethylphenoxy)-propyl]-3-piperidyl}-1-oxo-1,2,3,4-tetrahydroisoquinoline Hydrochloride (10h): (61%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.76−1.99 (4H, m), 2.21−2.28 (2H, m), 2.86−2.93 (3H, m), 3.17−3.25 (3H, m), 3.41−3.51 (4H, m), 3.77 (3H, s), 3.82 (3H, s), 4.16 (2H, t, J = 6.0 Hz), 4.87−4.93 (1H, m), 6.90 (1H, s), 7.14 (2H, d, J = 8.8 Hz), 7.38 (1H, s), 7.67 (2H, d, J = 8.8 Hz), 10.54 (1H, br s); MS (FAB) *m/z* 493 (MH^+). Anal. ($C_{26}H_{31}N_2O_4F_3$·HCl) C, H, N, Cl, F.

(±)-6,7-Dimethoxy-2-{1-[3-(4-fluorophenoxy)propyl]-3-piperidyl}-1-oxo-1,2,3,4-tetrahydroisoquinoline Hydrochloride (10i): (71%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.75−1.96 (4H, m), 2.17−2.21 (2H, m), 2.86−2.89 (3H, m), 3.16−3.24 (3H, m), 3.40−3.51 (4H, m), 3.77 (3H, s), 3.82 (3H, s), 4.04 (2H, t, J = 6.0 Hz), 4.88 (1H, br s), 6.90 (1H, s), 6.94−6.98 (2H, m), 7.10−7.16 (2H, m), 7.38 (1H, s), 10.33 (1H, br s); MS (FAB) *m/z* 443 (MH^+). Anal. ($C_{25}H_{31}N_2O_4F_3$·HCl·0.2H_2O) C, H, N, Cl, F.

(±)-2-{1-[3-(4-Chlorophenoxy)propyl]-3-piperidyl}-6,7-dimethoxy-1-oxo-1,2,3,4-tetrahydroisoquinoline Hydrochloride (10j): (75%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.75−1.95 (4H, m), 2.19−2.23 (2H, m), 2.86−2.89 (3H, m), 3.17−3.22 (3H, m), 3.39−3.49 (4H, m), 3.77 (3H, s), 3.82 (3H, s), 4.06 (2H, t, J = 6.0 Hz), 4.87−4.93 (1H, m), 6.90 (1H, s), 6.97 (2H, dt, J = 10.4, 2.4 Hz), 7.34 (2H, dt, J = 10.4, 2.4 Hz), 7.38 (1H, s), 10.59 (1H, br s); MS (FAB) *m/z* 459 (MH^+). Anal. ($C_{25}H_{31}N_2O_4Cl$·HCl) C, H, N, Cl.

(±)-2-{1-[3-(4-Bromophenoxy)propyl]-3-piperidyl}-6,7-dimethoxy- -1-oxo-1,2,3,4-tetrahydroisoquinoline Hydrochloride (10k): (40%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.75−1.95 (4H, m), 2.17−2.24 (2H, m), 2.86−2.89 (3H, m), 3.17−3.24 (3H, m), 3.39−3.50 (4H, m), 3.77 (3H, s), 3.82 (3H, s), 4.06 (2H, t, J = 6.0 Hz), 4.86−4.92 (1H, m), 6.90 (1H, s), 6.93 (2H, dt, J = 10.4, 2.8 Hz), 7.38 (1H, s), 7.46 (2H, dt, J = 10.4, 3.2 Hz), 10.54 (1H, br s); MS (FAB) *m/z* 503 (MH^+), 505 (MH^+ + 2). Anal. ($C_{25}H_{31}N_2O_4Br$·HCl) C, H, N, Br, Cl.

(±)-6,7-Dimethoxy-2-{1-[3-(4-methylphenoxy)propyl]-3-piperidyl}-1-oxo-1,2,3,4-tetrahydroisoquinoline Hydrochloride (10l): (70%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.75−1.95 (4H, m), 2.17−2.20 (2H, m), 2.23 (3H, s), 2.86−2.89 (3H, m), 3.17−3.22 (3H, m), 3.39−3.50 (4H, m), 3.77 (3H, s), 3.81 (3H, s), 4.01 (2H, t, J = 6.0 Hz), 4.86−4.89 (1H, m), 6.83 (2H, d, J = 8.8 Hz), 6.90 (1H, s), 7.09 (2H, d, J = 8.4 Hz), 7.38 (1H, s), 10.52 (1H, br s); MS (FAB) *m/z* 439 (MH^+). Anal. ($C_{26}H_{34}N_2O_4$·HCl·0.2H_2O) C, H, N, Cl.

(±)-6,7-Dimethoxy-2-{1-[3-(4-ethoxyphenoxy)propyl]-3-piperidyl}-1-oxo-1,2,3,4-tetrahydroisoquinoline Hydrochloride (10m): (67%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.29 (3H, t, J = 6.8 Hz), 1.74−1.95 (4H, m), 2.16−2.19 (2H, m), 2.86−2.89 (3H, m), 3.16−3.30 (3H, m), 3.39−3.50 (4H, m), 3.77 (3H, s), 3.81 (3H, s), 3.94 (2H, q, J = 6.8 Hz), 3.99 (2H, t, J = 6.0 Hz), 4.86−4.92 (1H, m), 6.83−6.88 (4H,m), 6.90 (1H, s), 7.38 (1H, s), 10.40 (1H, br s); MS (FAB) *m/z* 469 (MH^+). Anal. ($C_{27}H_{36}N_2O_5$·HCl) C, H, N, Cl.

(±)-6,7-Dimethoxy-2-{1-[3-(4-propoxyphenoxy)propyl]-3-piperidyl}-1-oxo-1,2,3,4-tetrahydroisoquinoline Hydrochloride (10n): (80%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.96 (3H, t, J = 7.6 Hz), 1.64−1.73 (2H, m), 1.75−1.95 (4H, m), 2.18 (2H, br s), 2.86−2.89 (3H, m), 3.20−3.22 (3H, m), 3.39−3.48 (4H, m), 3.77 (3H, s), 3.82 (3H, s), 3.84 (2H, t, J = 6.8 Hz), 3.99 (2H, t, J = 6.0 Hz), 4.89 (1H, br s), 6.86 (4H, s), 6.90 (1H, s), 7.38 (1H, s), 10.55 (1H, br s); MS (FAB) *m/z* 483 (MH^+). Anal. ($C_{28}H_{38}N_2O_5$·HCl·0.1H_2O) C, H, N, Cl.

(±)-6,7-Dimethoxy-2-{1-[3-(4-isopropoxyphenoxy)propyl]-3-piperidyl}-1-oxo-1,2,3,4-tetrahydroisoquinoline Hydrochloride (10o): (84%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.21 (3H, s), 1.22 (3H, s), 1.75−1.95 (4H, m), 2.14−2.21 (2H, m), 2.86−2.89 (3H, m), 3.16−3.24 (3H, m), 3.39−3.50 (4H, m), 3.77 (3H, s), 3.82 (3H, s), 3.99 (2H, t, J = 6.4 Hz), 4.42−4.51 (1H, m), 4.86−4.92 (1H, m), 6.85 (4H, s), 6.90 (1H, s), 7.38 (1H, s), 10.44 (1H, br s); MS (FAB) *m/z* 483 (MH^+). Anal. ($C_{28}H_{38}N_2O_5$·HCl) C, H, N, Cl.

(±)-2-{1-[3-(4-Benzyloxyphenoxy)propyl]-3-piperidyl}-6,7-dimethoxy-1-oxo-1,2,3,4-tetrahydroisoquinoline Hydrochloride (10p): (91%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.74−1.95 (4H, m), 2.18 (2H, br s), 2.86−2.89 (3H, m), 3.17−3.22 (3H, m), 3.39−3.49 (4H, m), 3.77 (3H, s), 3.81 (3H, s), 4.01 (2H, t, J = 6.4 Hz), 4.87−4.92 (1H, m), 5.03 (2H, s), 6.87−6.90 (3H, m), 6.92−6.96 (2H, m), 7.30−7.44 (6H, m), 10.54 (1H, br s); MS (FAB) *m/z* 531 (MH^+). Anal. ($C_{32}H_{38}N_2O_5$·HCl) C, H, N, Cl.

(±)-6,7-Dimethoxy-2-{1-[3-(4-Acetamidophenoxy)propyl]-3-piperidyl}-1-oxo-1,2,3,4-tetrahydroisoquinoline Hydrochloride (10q): (67%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.74−1.95 (4H, m), 2.00 (3H, s), 2.19 (2H, br s), 2.86−2.89 (3H, m), 3.16−3.24 (3H, m), 3.40−3.50 (4H, m), 3.77 (3H, s), 3.81 (3H, s), 4.01 (2H, t, J = 6.0 Hz), 4.86−4.92 (1H, m), 6.87 (2H, d, J = 8.8 Hz), 6.90 (1H, s), 7.38 (1H, s), 7.49 (2H, d, J = 9.2 Hz), 9.86 (1H, s), 10.40 (1H, br s); MS (FAB) *m/z* 482 (MH^+). Anal. ($C_{27}H_{35}N_3O_5$·HCl) C, H, N, Cl.

(±)-6,7-Dimethoxy-2-{1-[3-(4-methoxycarbonylphenoxy)-propyl]-3-piperidyl}-1-oxo-1,2,3,4-tetrahydroisoquinoline Hydrochloride (10r): (65%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.75−1.95 (4H, m), 2.24−2.27 (2H, m), 2.86−2.89 (3H, m), 3.18−3.26 (3H, m), 3.40−3.50 (4H, m), 3.77 (3H, s), 3.81 (3H, s), 3.82 (3H, s), 4.16 (2H, t, J = 6.4 Hz), 4.88−4.94 (1H, m), 6.90 (1H, s), 7.06 (2H, d, J = 8.8 Hz), 7.38 (1H, s), 7.92 (2H, d, J = 8.4 Hz), 10.72 (1H, br s); MS (FAB) *m/z* 483 (MH^+). Anal. ($C_{27}H_{34}N_2O_6$·HCl) C, H, N, Cl.

(±)-2-{1-[3-(4-Aminocarbonylphenoxy)propyl]-3-piperidyl}-6,7-dimethoxy-1-oxo-1,2,3,4-tetrahydroisoquinoline Hydrochloride (10s): (33%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.75−1.96 (4H, m), 2.23 (2H, br s), 2.86−2.93 (3H, m), 3.17−3.25 (3H, m), 3.41−3.51 (4H, m), 3.77 (3H, s), 3.82 (3H, s), 4.13 (2H, t, J = 6.0 Hz), 4.89 (1H, br s), 6.90 (1H, s), 6.99 (2H, d, J = 8.8 Hz), 7.20 (1H, br s), 7.38 (1H, s), 7.85−7.87 (3H, m), 10.44 (1H, br s); MS (FAB) *m/z* 468 (MH^+). Anal. ($C_{26}H_{33}N_3O_5$·HCl·0.6H_2O) C, H, N, Cl.

(±)-6,7-Dimethoxy-2-{1-[3-(3,4-dimethoxyphenoxy)propyl]-3-piperidyl}-1-oxo-1,2,3,4-tetrahydroisoquinoline Hydrochloride (10t): (88%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.75−1.99 (4H, m), 2.15−2.22 (2H, m), 2.86−2.90 (3H, m), 3.17−3.25 (3H, m), 3.40−3.50 (4H, m), 3.68 (3H, s), 3.74 (3H, s), 3.77 (3H, s), 3.82 (3H, s), 4.00 (2H, t, J = 6.4 Hz), 4.87−4.93 (1H, m), 6.44 (1H, dd, J = 8.8, 2.8 Hz), 6.57 (1H, d, J = 2.8 Hz), 6.85 (1H, d, J = 10.0 Hz), 6.90 (1H, s), 7.38 (1H, s), 10.48 (1H, br s); MS (FAB) *m/z* 485 (MH^+). Anal. ($C_{27}H_{36}N_2O_6$·HCl) C, H, N, Cl.

(±)-6,7-Dimethoxy-2-{1-[3-(3,4-ethylenedioxyphenoxy)-propyl]-3-piperidyl}-1-oxo-1,2,3,4-tetrahydroisoquinoline Hydrochloride (10u): (81%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.75−1.94 (4H, m), 2.17 (2H, br s), 2.88 (3H, br s), 3.19−3.22 (3H, m), 3.38−3.48 (4H, m), 3.77 (3H, s), 3.82 (3H, s), 3.96 (2H, t, J = 6.4 Hz), 4.16−4.17 (2H, m), 4.20−4.21 (2H, m), 4.89 (1H, br s), 6.42 (1H, dd, J = 8.8, 2.8 Hz), 6.47 (1H, d, J = 2.8 Hz), 6.76 (1H, d, J = 8.8 Hz), 6.90 (1H, s), 7.38 (1H, s), 10.61 (1H, br s); MS (FAB) *m/z* 483 (MH^+). Anal. ($C_{27}H_{34}N_2O_6$·HCl) C, H, N, Cl.

(±)-6,7-Dimethoxy-2-{1-[3-(3,4,5-trimethoxyphenoxy)-propyl]-3-piperidyl}-1-oxo-1,2,3,4-tetrahydroisoquinoline Hydrochloride (10v): (63%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.75−1.96 (4H, m), 2.17−2.19 (2H, m), 2.86−2.90 (3H, m), 3.17−3.25 (3H, m), 3.41−3.50 (4H, m), 3.57 (3H, s), 3.76 (6H, s), 3.77 (3H, s), 3.82 (3H, s), 4.05 (2H, t, J = 6.4 Hz), 4.87−4.93 (1H, m), 6.25 (2H, s), 6.90 (1H, s), 7.38 (1H, s), 10.52 (1H, br s); MS (FAB) m/z 515 (MH^+). Anal. ($C_{28}H_{38}N_2O_7$·HCl·0.3H_2O) C, H, N, Cl.

(±)-6,7-Dimethoxy-2-{1-[3-(5-indanyloxy)propyl]-3-piperidyl}-1-oxo-1,2,3,4-tetrahydroisoquinoline Hydrochloride (10w): (70%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.74−2.03 (6H, m), 2.15−2.22 (2H, m), 2.77(2H, t, J = 8.0 Hz), 2.81 (2H, t, J = 7.6 Hz), 2.86−2.89 (3H, m), 3.16−3.24 (3H, m), 3.39−3.50 (4H, m), 3.77 (3H, s), 3.82 (3H, s), 4.01 (2H, t, J = 6.4 Hz), 4.86−4.92 (1H, m), 6.69 (1H, dd, J = 8.4, 2.4 Hz), 6.82 (1H, d, J = 2.4 Hz), 6.90 (1H, s), 7.11 (1H, d, J = 8.0 Hz), 7.38 (1H, s), 10.39 (1H, br s); MS (FAB) m/z 465 (MH^+). Anal. ($C_{28}H_{36}N_2O_4$·HCl) C, H, N, Cl.

(±)-6,7-Dimethoxy-2-{1-[3-(5-indoloxy)propyl]-3-piperidyl}-1-oxo-1,2,3,4-tetrahydroisoquinoline Hydrochloride (10x): (70%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.75−1.96 (4H, m), 2.21 (2H, br s), 2.86−2.89 (3H, m), 3.18−3.26 (3H, m), 3.42−3.52 (4H, m), 3.77 (3H, s), 3.82 (3H, s), 4.04 (2H, t, J = 6.4 Hz), 4.87−4.93 (1H, m), 6.32 (1H, t, J = 2.0 Hz), 6.74 (1H, dd, J = 8.8, 2.4 Hz), 6.90 (1H, s), 7.06 (1H, d, J = 2.0 Hz), 7.27−7.29 (2H, m), 7.38 (1H, s), 10.42 (1H, br s), 10.96 (1H, s); MS (FAB) m/z 464 (MH^+). Anal. ($C_{27}H_{33}N_3O_5$·HCl·0.8H_2O) C, H, N, Cl.

(±)-6,7-Dimethoxy-2-{1-[3-(4-hydroxyphenoxy)propyl]-3-piperidyl}-1-oxo-1,2,3,4-tetrahydroisoquinoline Hydrochloride (11). To a solution of **10p** (486 mg, 0.856 mmol) in MeOH−H_2O (10 mL) was added Pd/C (10 w/w %, 49 mg), and the mixture was stirred under hydrogen atmosphere at room temperature for 5 h. The catalyst was removed by filtration and the filtrate was concentrated in vacuo. The residual solid was recrystallized from *i*-PrOH-MeOH to give **11** (315 mg, 77%) as a colorless powder: mp 215−220 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.74−1.95 (4H, m), 2.17 (2H, br s), 2.86−2.89 (3H, m), 3.17−3.22 (3H, m), 3.39−3.48 (4H, m), 3.77 (3H, s), 3.82 (3H, s), 3.94 (2H, t, J = 5.6 Hz), 4.87−4.93 (1H, m), 6.69 (2H, dt, J = 9.6, 3.2 Hz), 6.76 (2H, dt, J = 10.0, 3.2 Hz), 6.90 (1H, s), 7.36 (1H, s), 9.00 (1H, s), 10.56 (1H, br s); MS (FAB) m/z 441 (MH^+). Anal. ($C_{25}H_{32}N_2O_5$·HCl·0.6H_2O) C, H, N, Cl. Cl calcd 7.27 found 6.82.

(±)-2-{1-[3-(4-Aminophenoxy)propyl]-3-piperidyl}-6,7-dimethoxy-1-oxo-1,2,3,4-tetrahydroisoquinoline Hydrochloride (12): prepared from **10f** by a procedure similar to that described for **11** (64%): mp 223−231 °C (from AcOEt−EtOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.73−1.92 (4H, m), 2.10−2.13 (2H, m), 2.81−2.83 (3H, m), 2.86−2.89 (3H, m), 3.16 (3H, br s), 3.33−3.48 (4H, m), 3.77 (3H, s), 3.81 (3H, s), 3.91 (2H, t, J = 6.4 Hz), 4.85 (1H, br s), 6.57 (2H, d, J = 8.4 Hz), 6.69 (2H, d, J = 8.8 Hz), 6.89 (1H, s), 7.38 (1H, s), 10.38 (1H, br s); MS (FAB) m/z 440 (MH^+). Anal. ($C_{25}H_{33}N_3O_4$·HCl) C, H, N, Cl.

(±)-*N*-(1-Benzyl-3-piperidyl)-*N*′-(2,2-dimethoxyethyl)-3,4-dimethoxybenzamide (13). To a suspension of **5** (4.51 g, 20.0 mmol) and aminoacetaldehyde dimethylacetal (2.10 g, 20.0 mmol) in THF (50 mL) were added AcOH (2.29 mL, 40.0 mmol) and $NaBH(OAc)_3$ (5.09 g, 24.0 mmol), and the mixture was stirred room temperature for 3 h. The mixture was made alkaline with 5 N NaOH aq at 0 °C, then extracted with $CHCl_3$ (40 mL × 2). The combined extract was dried and concentrated in vacuo to give 1-benzyl-3-[(2,2-dimethoxyethyl)amino]piperidine (4.12 g) as a brown oil. To a solution of compound obtained above (1.39 g, 5.00 mmol) and Et_3N (0.767 mL, 5.50 mmol) in THF (20 mL) was added dropwise a solution of 3,4-dimethoxybenzoyl chloride (1.05 g, 5.25 mmol) in THF (5 mL) at 0 °C, and the mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated in vacuo and the residue was dissolved in H_2O (50 mL), then extracted with AcOEt (30 mL × 2). The combined extract was washed with 1 N NaOH aq (30 mL) and was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 99/1) to give **13** (2.11 g, 70% from **5**) as a brown oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51−1.89 (4H, m), 2.10 (2H, br s), 2.74−2.84 (2H, m), 3.34−3.68 (10H, m), 3.80 (3H, s), 3.91 (1H, br s), 3.92 (3H, s), 4.65 (1H, br s), 6.81−6.88 (3H, m), 7.24−7.33 (5H, m); MS (FAB) m/z 443 (MH^+).

(±)-2-(1-Benzyl-3-piperidyl)-6,7-dimethoxy-1-oxo-1,2-dihydroisoquinoline (14). To a solution of **13** (2.10 g, 4.75 mmol) in AcOH (5 mL) was added c.HCl (5 mL), and the mixture was stirred at room temperature for 24 h. The mixture was poured into H_2O (30 mL) and made alkaline with 5 N NaOH aq at 0 °C, then extracted with $CHCl_3$ (30 mL × 2). The combined extract was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 49/1) to give **14** (1.13 g, 52%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.64−1.80 (3H, m), 1.93−1.96 (1H, m), 2.18 (1H, br s), 2.31−2.36 (1H, m), 2.77−2.80 (1H, m), 2.97−2.99 (1H, m), 3.57 (2H, s), 3.98 (3H, s), 3.99 (3H, s), 5.15−5.19 (1H, m), 6.40 (1H, d, J = 7.2 Hz), 6.72 (1H, s), 7.24−7.37 (6H, m), 7.80 (1H, s); MS (FAB) m/z 379 (MH^+).

(±)-6,7-Dimethoxy-1-oxo-2-(3-piperidyl)-1,2-dihydroisoquinoline Hydrochloride (15). To a solution of **14** (1.10 g, 2.91 mmol) in AcOEt (10 mL) was added 4 N HCl (g)/AcOEt (0.873 mL, 3.49 mmol), and the mixture was concentrated in vacuo. To a solution of the residual solid in AcOH (10 mL) was added Pd/C (10 w/w %, 110 mg), and the mixture was stirred under hydrogen pressure (3−4 kg/cm^2) at room temperature for 2 days. The catalyst was removed by filtration and the filtrate was concentrated in vacuo. The residue was dissolved in H_2O (20 mL) and made alkaline with 5 N NaOH aq at 0 °C, then extracted with $CHCl_3$ (20 mL × 2). The combined extract was dried and concentrated in vacuo to give the free base of **15** (811 mg, 97%) as a slightly yellow oil. This material was converted to its hydrochloride salt by treating with 4 N HCl (g)/AcOEt (1.05 mL, 4.22 mmol). The crude salt was recrystallized from CH_3CN to give **15** (600 mg, 64%) as a slightly yellow powder: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.84−2.09 (4H, m), 2.87 (1H, br s), 3.27−3.29 (3H, m), 3.86 (3H, s), 3.89 (3H, s), 5.21−5.22 (1H, m), 6.63 (1H, d, J = 7.6 Hz), 7.17 (1H, s), 7.46 (1H, d, J = 7.6 Hz), 7.59 (1H, s), 9.13 (1H, br s), 9.59 (1H, br s); MS (FAB) m/z 289 (MH^+).

(±)-6,7-Dimethoxy-2-{1-[3-(3,4-methylenedioxyphenoxy)-propyl]-3-piperidyl}-1-oxo-1,2-dihydroisoquinoline Hydrochloride (16): prepared from **15** by a procedure similar to that described for **10a** (67%): mp 205−208 °C (from AcOEt−CH_3CN); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.89−2.21 (6H, m), 2.97−3.00 (1H, m), 3.23−3.57 (5H, m), 3.86 (3H, s), 3.89 (3H, s), 3.98 (2H, t, J = 6.0 Hz), 5.32 (1H, br s), 5.95 (2H, s), 6.38 (1H, dd, J = 8.0, 2.4 Hz), 6.63−6.66 (2H, m), 6.81 (1H, d, J = 8.4 Hz), 7.17 (1H, s), 7.40 (1H, d, J = 7.2 Hz), 7.59 (1H, s), 10.76 (1H, br s); MS (FAB) m/z 467 (MH^+). Anal. ($C_{26}H_{30}N_2O_6$·HCl) C, H, N, Cl.

1-[3-(3,4-Methylenedioxyphenoxy)propyl]-3-piperidone (17). To a solution of (±)-3-hydroxypiperidine (1.21 g, 12.0 mmol) in CH_3CN (15 mL) were added K_2CO_3 (1.82 g, 13.2 mmol) and **9a** (3.26 g, 12.6 mmol), and the mixture was stirred at 80 °C for 4 h. After being cooled at room temperature, the mixture was concentrated in vacuo. The residue was partitioned between $CHCl_3$ (40 mL × 2) and H_2O (40 mL), then the $CHCl_3$ layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 24/1) to give (±)-3-hydroxy-1-[3-(3,4-methylenedioxyphenoxy)propyl]piperidine (3.35 g, 12.0 mmol). To a cooled (−70 °C) solution of $(COCl)_2$ (2.06 mL, 24.0 mmol) in CH_2Cl_2 (20 mL) was added dropwise a solution of DMSO (2.13 mL, 30.0 mmol) in CH_2Cl_2 (5 mL), and the mixture was stirred at −70 °C for 10 min. To the mixture was added dropwise a solution of compound obtained above (3.35 g, 12.0 mmol) in CH_2Cl_2 (10 mL) at −70 °C, and the mixture was stirred at ambient temperature for 1 h. To the mixture was added Et_3N (6.69 mL, 48.0 mmol), and the mixture was allowed to warm and stir at 0 °C for 1 h. To the mixture was added sat. $NaHCO_3$ aq (20 mL), and the mixture was partitioned between $CHCl_3$

(30 mL × 2) and H_2O (40 mL). The $CHCl_3$ layer was dried and concentrated in vacuo to give **17** (3.40 g, 99%) as a light yellow oil. This compound was used in the next step without further purification.

(±)-3-Amino-1-[3-(3,4-methylenedioxyphenoxy)propyl]-piperidine (18). To a solution of **17** (3.40 g, 12.0 mmol) in pyridine (30 mL) was added *O*-benzylhydroxylamine hydrochloride (2.11 g, 13.2 mmol), and the mixture was stirred at room temperature for 18 h, then concentrated in vacuo. After coevaporated with toluene, the residue was partitioned between $CHCl_3$ (30 mL × 2) and 0.2 N NaOH aq (40 mL). The $CHCl_3$ layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 49/1) to give *O*-benzyl 1-[3-(3,4-methylenedioxyphenoxy)propyl]-3-piperidone oxime (4.44 g, 11.6 mmol) as a yellow oil. To a suspension of $LiAlH_4$ (1.10 g, 29.0 mmol) in THF (20 mL) was added a solution of compound obtained above (4.44 g, 11.6 mmol) in THF (10 mL), and the mixture was stirred under reflux for 1 h. After being cooled at room temperature, to the cooled (−40 °C) mixture were added dropwise H_2O (3 mL), 1 N NaOH aq (3 mL), and H_2O (3 mL), then the mixture was stirred at room temperature for 2 h. The precipitate was filtered off, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 22/3) to give **18** (1.93 g, 60%) as a light yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05−1.17 (1H, m), 1.49−1.98 (6H, m), 2.02−2.08 (1H, m), 2.46−2.51 (2H, m), 2.64−2.67 (1H, m), 2.78−2.93 (2H, m), 3.93 (2H, t, J = 6.3 Hz), 5.90 (2H, s), 6.32 (1H, dd, J = 8.4, 2.4 Hz), 6.49 (1H, d, J = 2.4 Hz), 6.69 (1H, d, J = 8.4 Hz); MS (FAB) m/z 279 (MH^+).

(±)-3-Methylamino-1-[3-(3,4-methylenedioxyphenoxy)-propyl]piperidine (19). To a solution of **17** (416 mg, 1.50 mmol) and 40% $MeNH_2$/MeOH (349 mg, 4.50 mmol) in THF (10 mL) were added AcOH (0.258 mL, 4.50 mmol) and $NaBH(OAc)_3$ (413 mg, 1.95 mmol) at 0 °C, and the mixture was stirred at room temperature for 17 h. The reaction mixture was made alkaline with 1 N NaOH aq at 0 °C, then extracted with $CHCl_3$ (15 mL × 2). The combined extract was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 22/3) to give **19** (286 mg, 65%) as a slightly yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27−1.30 (1H, m), 1.51−2.23 (7H, m), 2.32 (2H, br s), 2.47 (3H, s), 2.51−2.53 (2H, m), 2.65−2.79 (2H, m), 2.85−2.89 (1H, m), 3.93 (2H, t, J = 6.3 Hz), 5.90 (2H, s), 6.32 (1H, dd, J = 8.4, 2.4 Hz), 6.49 (1H, d, J = 2.4 Hz), 6.69 (1H, d, J = 8.4 Hz); MS (FAB) m/z 293 (MH^+).

(±)-6,7-Dimethoxy-3-{1-[3-(3,4-methylenedioxyphenoxy)-propyl]-3-piperidyl}-4-oxo-3,4-dihydroquinazoline Hydrochloride (20). To a solution of **18** (418 mg, 1.50 mmol) in $Cl(CH_2)_2Cl$ (8 mL) were added HOBt (101 mg, 0.750 mmol), EDC·HCl (316 mg, 1.65 mmol), and 4,5-dimethoxyanthranilic acid (311 mg, 1.58 mmol) at 0 °C, and the mixture was stirred at room temperature for 6 h. The mixture was partitioned between $CHCl_3$ (20 mL × 2) and H_2O (30 mL), and the $CHCl_3$ layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 49/1) to give (±)-2-amino-4,5-dimethoxy-*N*-{1-[3- (3,4-methylenedioxyphenoxy)propyl]-3-piperidyl}benzamide (623 mg, 1.36 mmol) as a yellow oil. A solution of compound obtained above (613 mg, 1.34 mmol) in $HC(OEt)_3$ (8 mL) was stirred under reflux for 21 h. After being cooled at room temperature, the mixture was concentrated in vacuo and the residue was partitioned between $CHCl_3$ (20 mL × 2) and H_2O (30 mL), and the $CHCl_3$ layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 49/1) to give the free base of **20** (545 mg, 87%) as a slightly yellow oil. This material was converted to its hydrochloride salt by treating with 4 N HCl (g)/AcOEt (0.350 mL, 1.40 mmol). The crude salt was recrystallized from AcOEt−CH_3CN to give **20** (300 mg, 44%) as a slightly yellow powder: mp 142−146 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.98−2.04 (3H, m), 2.16−2.19 (3H, m), 2.96−2.99 (1H, m), 3.23−3.26 (2H, m), 3.48−3.58 (2H, m), 3.69 (1H, br s), 3.88 (3H, s), 3.92 (3H, s), 3.99 (2H, t, J = 6.0 Hz), 5.16 (1H, br s), 5.95 (2H, s), 6.38 (1H, dd, J = 8.4, 2.4 Hz), 6.63 (1H, d, J = 2.4 Hz), 6.81 (1H, d, J = 8.8 Hz), 7.16 (1H, s), 7.46 (1H, s), 8.33 (1H, s), 10.85 (1H, br s); MS (FAB) m/z 468 (MH^+). Anal. ($C_{25}H_{29}N_3O_6$·HCl·1.5H_2O) C, H, N, Cl.

(±)-3,4-Dimethoxy-*N*-{1-[3-(3,4-methylenedioxyphenoxy)-propyl]-3-piperidyl}benzamide Hydrochloride (21). To a solution of **18** (167 mg, 0.600 mmol) in AcOEt (3 mL) was added a solution of 3,4-dimethoxybenzoyl chloride (126 mg, 0.630 mmol) in AcOEt (2 mL) at 0 °C, and the mixture was stirred at room temperature for 14 h. The mixture was partitioned between AcOEt (15 mL × 2) and 1 N NaOH aq (30 mL), and the AcOEt layer was washed with sat.NaCl (20 mL), then dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 49/1) to give the free base of **21** (266 mg, 100%) as a slightly yellow oil. This material was converted to its hydrochloride salt by treating with 4 N HCl (g)/AcOEt (0.180 mL, 0.720 mmol). The crude salt was recrystallized from EtOH−Et_2O to give **21** (188 mg, 65%) as a slightly pink powder: mp 165−167 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.60−1.93 (4H, m), 2.13−2.22 (2H, m), 2.75−2.99 (2H, m), 3.26 (2H, br s), 3.50−3.59 (2H, m), 3.81−3.85 (6H, m), 3.96−3.99 (2H, m), 4.28 (2/3H, br s), 4.49 (1/3H, br s), 5.96 (2H, s), 6.37−6.40 (1H, m), 6.65 (1H, t, J = 2.4 Hz), 6.81 (1H, dd, J = 8.4, 3.6 Hz), 7.02 (1H, t, J = 8.8 Hz), 7.45−7.71 (2H, m), 8.44 (2/3H, d, J = 8.0 Hz), 8.95 (1/3H, d, J = 7.6 Hz), 10.20 (2/3H, br s), 11.11 (1/3H, br s); MS (FAB) m/z 443 (MH^+). Anal. ($C_{24}H_{30}N_2O_6$·HCl) C, H, N, Cl.

(±)-3,4-Dimethoxy-*N*-methyl-*N*′-{1-[3-(3,4-methylenedioxyphenoxy)propyl]-3-piperidyl}benzamide Hydrochloride (22): prepared from **19** by a procedure similar to that described for **21** (58%): mp 178−181 °C (from EtOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.82−1.94 (4H, m), 2.14 (2H, br s), 2.85 (3H, s), 2.87 (2H, br s), 3.19−3.22 (4H, m), 3.48−3.51 (1H, m), 3.78 (3H, s), 3.79 (3H, s), 3.98 (2H, t, J = 6.0 Hz), 5.96 (2H, s), 6.38 (1H, dd, J = 8.8, 2.8 Hz), 6.64 (1H, d J = 2.8 Hz), 6.82 (1H, d, J = 8.0 Hz), 6.99−7.02 (3H, m), 10.20 (1H, br s); MS (FAB) m/z 457 (MH^+). Anal. ($C_{25}H_{32}N_2O_6$·HCl) C, H, N, Cl.

(±)-*N*-(1-*tert*-Butoxycarbonyl-3-piperidyl)-3,4-dimethoxy-6-(ethoxycarbonylamino)benzamide (25). To a solution of *tert*-butyl 3-aminopiperidin-1-carboxylate (**24**)[21] in pyridine (15 mL) was added 6,7-dimethoxy-2-ethoxy-4-oxo-1,3-benzoxazin **23**[22] (1.26 g, 5.00 mmol), and the mixture was stirred at 120 °C for 2 h. After being cooled at room temperature, the mixture was concentrated in vacuo. The residue was partitioned between $CHCl_3$ (30 mL × 2) and 5% (w/v) citric acid aq (30 mL), and the $CHCl_3$ layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/AcOEt = 1/2) to give **25** (1.95 g, 86%) as a colorless foam:^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (3H, t, J = 7.2 Hz), 1.45 (9H, s), 1.66−2.04 (4H, m), 3.25−3.76 (4H, m), 3.88 (3H, s), 3.95 (3H, s), 4.05 (1H, br s), 4.13−4.23 (2H, m), 6.89 (1H, br s), 8.11 (1H, s), 10.74 (1H, br s); MS (FAB) m/z 452 (MH^+).

(±)-6,7-Dimethoxy-2,4-dioxo-3-(3-piperidyl)-1,2,3,4-tetrahydroquinazoline Hydrochloride (26). To a suspension of NaH (60%, 344 mg, 8.59 mmol) in DMF (30 mL) was added dropwise a solution of **25** (1.94 g, 4.30 mmol) in DMF (10 mL), and the mixture was stirred at 50 °C for 12 h. After being cooled at room temperature, to the mixture was added H_2O (50 mL), then extracted with $CHCl_3$ (40 mL × 2). The combined extract was dried and concentrated in vacuo. The residual solid was recrystallized from AcOEt−hexane to give (±)-3-(1-*tert*-butoxycarbonyl-3-piperidyl)-6,7-dimethoxy-2,4-dioxo-1,2,3,4-tetrahydroquinazoline (1.19 g, 2.93 mmol) as a beige powder. To a solution of the compound obtained above in MeOH (5 mL) was added 4 N HCl (g)/AcOEt (3.63 mL, 14.5 mmol), and the mixture was stirred at room temperature for 10 h. The mixture was concentrated in vacuo, and the residual solid was recrystallized from MeOH to give **26** (850 mg, 58% from **25**) as a colorless powder:^{1}H NMR (400 MHz, DMSO-d_6) δ 1.73−1.79 (2H, m), 1.91−1.94 (1H, m), 2.41−2.47 (1H, m), 2.76−2.79 (1H, m), 3.24−3.29 (2H, m), 3.73−3.76 (1H, m), 3.79 (3H, s), 3.83

(3H, s), 5.14−5.20 (1H, m), 6.71 (1H, s), 7.27 (1H, s), 8.98 (1H, br s), 9.40 (1H, br s), 11.33 (1H, s); MS (FAB) *m*/*z* 306 (MH^+).

(±)-6,7-Dimethoxy-3-{1-[3-(3,4-methylenedioxyphenoxy)-propyl]-3-piperidyl}-2,4-dioxo-1,2,3,4-tetrahydroquinazoline Hydrochloride (27): prepared from **26** by a procedure similar to that described for **10a** (45%): mp 227−233 °C (from CH_3-CN-MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.76−1.78 (1H, m), 1.96 (2H, br s), 2.08 (2H, br s), 2.41−2.50 (1H, m), 2.92−2.95 (1H, m), 3.25−3.30 (3H, m), 3.51−3.65 (2H, m), 3.79 (3H, s), 3.83 (3H, s), 3.97 (2H, t, J = 6.0 Hz), 5.31 (1H, br s), 5.95 (2H, s), 6.38 (1H, dd, J = 8.4, 2.8 Hz), 6.63 (1H, d, J = 2.4 Hz), 6.71 (1H, s), 6.81 (1H, d, J = 8.4 Hz), 7.26 (1H, s), 10.64 (1H, br s), 11.37 (1H, s); MS (FAB) *m*/*z* 484 (MH^+). Anal. ($C_{25}H_{29}N_3O_7$·HCl·0.4H_2O) C, H, N, Cl.

(*S*)-(−)-6,7-Dimethoxy-1-oxo-2-(3-piperidyl)-1,2,3,4-tetrahydroisoquinoline D-Tartrate ((*S*)-8) and (*R*)-(+)-6,7-Dimethoxy-1-oxo-2-(3-piperidyl)-1,2,3,4-tetrahydroisoquinoline L-Tartrate ((*R*)-8). To a solution of **8** (1.60 g, 5.51 mmol) in EtOH (20 mL) was added a solution of D-tartaric acid (826 mg, 5.51 mmol) in EtOH (8 mL), and the mixture was concentrated in vacuo. The residual solid was recrystallized four times from 95% (v/v) EtOH aq (25−50 mL) to give (*S*)-**8** (650 mg, 27%, t_R = 12.3 min., 99.8% ee) as a colorless powder: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.69−1.89 (4H, m), 2.70−2.76 (1H, m), 2.85 (2H, t, J = 6.4 Hz), 2.97−3.03 (1H, m), 3.12−3.19 (2H, m), 3.45 (2H, t, J = 6.4 Hz), 3.76 (3H, s), 3.81 (3H, s), 3.87 (2H, s), 4.72 (1H, br s), 6.89 (1H, s), 7.37 (1H, s); MS (FAB) *m*/*z* 291 (MH^+); $[\alpha]^{25}_D$ = −26.8° (*c* = 1.0, MeOH). The mother liquor of (*S*)-**8** was concentrated in vacuo. The residue was dissolved in H_2O and made alkaline with 1 N NaOH aq, then extracted with $CHCl_3$ (20 mL × 2). The combined extract was dried and concentrated in vacuo. To a solution of the residual oil in EtOH (10 mL) was added a solution of L-tartaric acid (320 mg, 2.13 mmol) in EtOH (6 mL), and the mixture was concentrated in vacuo. The residual solid was recrystallized two times from 95% (v/v) EtOH aq (30−50 mL) to give (*R*)-**8** (460 mg, 19%, t_R = 16.2 min., 99.7% ee) as a colorless powder: $[\alpha]^{25}_D$ = +28.8° (*c* = 1.0, MeOH). The ^{1}H NMR and mass spectra of (*R*)-**8** were identical to those observed for (*S*)-**8**.

(*S*)-(−)-6,7-Dimethoxy-2-{1-[3-(3,4-methylenedioxyphenoxy)propyl]-3-piperidyl}-1-oxo-1,2,3,4-tetrahydroisoquinoline Hydrochloride ((*S*)-10a): prepared from (*S*)-**8** by a procedure similar to that described for **10a** (81%, t_R = 23.8 min., >99.8% ee): mp 200−202 °C (from EtOH); $[\alpha]^{25}_D$ = −16.8° (*c* = 1.0, MeOH). Anal. ($C_{26}H_{32}N_2O_6$·HCl) C, H, N, Cl.

(*R*)-(+)-6,7-Dimethoxy-2-{1-[3-(3,4-methylenedioxyphenoxy)propyl]-3-piperidyl}-1-oxo-1,2,3,4-tetrahydroisoquinoline Hydrochloride ((*R*)-10a): prepared from (*R*)-**8** by a procedure similar to that described for **10a** (83%, t_R = 28.3 min., >99.8% ee): mp 190−194 °C (from EtOH); $[\alpha]^{25}_D$ = +16.6° (*c* = 1.0, MeOH). Anal. ($C_{26}H_{32}N_2O_6$·HCl·0.2H_2O) C, H, N, Cl.

Correlation Analyses. Three descriptors for aromatic substituents, namely, π, σ_p, and MR, were attempted in the correlation analyses for **10b**, **10e**−**o**, **10q**−**s**, **11**, and **12**. Data analyses were carried out using Microsoft Excel Version 2000 (Microsoft Corporation) running on Windows 2000.

Pharmacology. In Vitro Assay. Male Hartley guinea pigs (250−400 g) were sacrificed by cervical dislocation, and their hearts were removed rapidly. Right atrium were cut from the heart and mounted vertically in a 30 mL organ bath containing Tyrode's solution at 37 °C and equilibrated with 95% O_2 and 5% CO_2. Tension was placed on the atria by suspending a 1 g mass from it. The atria was allowed to equilibrate for 90 min, the bath solution was exchanged every 15 min before a compound treatment. Amplitude of contraction was measured isometrically by a force-displacement transducer (Nihon Kohden SB-1T) and measured with a cardiotachometer (Nihon Kohden AT-600G) triggered by the contraction. After initial spontaneous beat rates were recorded, a compound was added cumulatively to the bath solution at 45 min intervals, and a concentration−response curve was constructed. The effects of compounds were presented the percent change from the initial beat rates.

In Vivo Assay. General Procedure: Male Wister rats (270−350 g) were anesthetized with pentobarbital (1.0 g/kg ip for iv study, 60 mg/kg ip for po study). One polyethylene cannulae (PE-50) was implanted in the common carotid artery and one was implanted in the right jugular vein. The other ends of catheters were routed to an exit site at the back of the neck. Blood pressure was measured with a pressure transducer (Nihon Kohden DX-100) coupled to the cannula introduced into carotid artery and a pressure amplifier (Nihon Kohden AP-621G), and continuously recorded via a polygraph system. Mean blood pressure (MBP)[19] 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.

iv Study: After the general procedure, a test compound as an aqueous solution (or a saline) was administered intravenously through the catheter implanted into the jugular vein at a dose of 3 mg/kg (the salt form).

po Study: The animals were allowed to recover for 1 to 2 days after operation, during which time they were housed in individually with free access to rat chow and water. After a 30 min measurement period to establish baseline values, a test compound as an aqueous solution (or a saline) was administered orally by gavage at a dose of 10 mg/kg (the salt form).

Inhibitory Effect on I_f Currents. SA node cell dissociation: Male Hartley guinea pigs (250−400 g) were sacrificed by cervical dislocation, and their hearts were removed quickly and placed in Tyrode's solution. The SA node region was isolated and incubated in Ca^{2+}-free Tyrode's solution containing 3 mg/mL collagenase (Worthington Type II) at 37 °C for 30 min. After incubation, the tissue was placed in a KB recovery solution and agitated by suction using a blunt glass pipet to release single cells. Pacemaker cells isolated from SA node were transferred to a recording chamber on the stage of microscope (Nikon) and were perfused continuously with the external solution. Electrical recording of I_f current: Membrane currents were measured using a conventional whole-cell patch configuration. Recording electrodes were pulled from a glass tube with an inner filament (Narishige GD-1.5) using a micropipet puller (Sutter Instrument P-97/IVF), and were fired-polished on a microforge (Narishige MF-9). The electrodes had a resistance of about 3−5 MΩ when filled with the internal solution. Whole-cell membrane currents were recorded in voltage-clamp mode using a high-impedance patch clamp amplifir (Axon Instruments Axopatch 200A). Voltage clamp steps were controlled and applied by the pCLAMP version 6.0.3 software (Axon Instruments) via an analogue to digital conversion board (Axon Instruments Digidata 1200A) running on Windows 95. The currents were low-pass filtered at 1 kHz and were sampled at 1.25 kHz. All data were stored on the floppy disks. I_f currents were elicited by a hyperpolarization voltage step pulses from a holding potential of −40 mV to −120 mV for 1 s, which were applied to cells every 5 s. After recording stable I_f currents as control, the solution perfused to cells was changed to the external solution containing a test compound at a certain concentration, and then I_f currents were successively recorded for further 7−8 min. The inhibitory effect of a test compound on I_f currents was evaluated as a percent inhibition of the initial amplitude of I_f currents. Concentration−response relationship was constructed from the average of percent inhibition of I_f currents obtained from a single cell at each concentration.

External solution (Tyrode's solution) (mM): NaCl, 140; KCl, 5.4; $CaCl_2$, 1.8; $MgCl_2$, 0.5; HEPES, 5; glucose, 10. Ca^{2+}-free Tyrode's solution (mM): NaCl, 140; KCl, 5.4; $MgCl_2$, 3.5; HEPES, 5; glucose, 10; taurine, 20; EGTA, 0.05. KB recovery solution (mM): KCl, 70; HEPES, 5; glucose, 10; taurine, 20; K_2ATP, 5; $MgSO_4$, 5; KH_2PO_4, 20; glutamic acid, 5; creatine, 5; succinic acid, 5. Internal solution (mM): KCl, 140; $MgCl_2$,

3; HEPES, 11; K_2ATP, 3; GTP (Na salt), 0.4; triphosphocreatine, 5. All solution were adjusted to pH 7.2.

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