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Synthesis and pharmacological evaluation of *N*-acyl-1,2,3,4-tetrahydroisoquinoline derivatives as novel specific bradycardic agents

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Abstract—A series of *N*-acyl-1,2,3,4-tetrahydroisoquinoline derivatives were synthesized and evaluated for their bradycardic activities in isolated guinea pig right atria and in urethane-anesthetized rats. These efforts resulted in identification of the compound **8a**, which exhibits potent bradycardic activity with minimal influence on mean blood pressure in urethane-anesthetized rats. Oral administration of compound **8a** to conscious rats revealed increased potency and prolonged duration of action when compared to Zatebradine.

1. Introduction

Chronic increase in heart rate (HR) is thought to be a contributory factor in cardiovascular morbidity and mortality in patients with cardiac diseases such as ischemic heart diseases.[1] Sinus tachycardia is a common physiological response that may help to maintain homeostasis by increasing cardiac output, but that also causes an increase in myocardial oxygen demand and decrease in time for myocardial relaxation and diastolic ventricular filling.[2] In the presence of flow-limiting coronary artery stenosis a decrease in diastolic perfusion time may be especially deleterious by further reducing subendocardial myocardial perfusion.[3] Under these circumstances, a reduction in HR prolongs the diastolic perfusion time and reduces myocardial oxygen demands, conferring an improvement in ischemic zone perfusion and function. Reduction in HR can be achieved by β-adrenoreceptor antagonists[4] or certain calcium channel blockers.[5] However, these agents may cause concominant negative inotropic and hypotensive effects that are potentially deleterious during ischemia.[6] Therefore, agents which reduce HR without negative inotropic and hypotensive effects, namely 'specific bradycardic agents'[7] are expected to be more beneficial in the treatment of cardiovascular disorders such as ischemic heart disease.

In the last decade, two specific bradycadic agents, Zatebradine[8] and the related compound Ivabradine,[9] have been developed and subjected to clinical testing in ischemic heart disease (Fig. 1).

In the pursuit of novel specific bradycardic agents, 2-(3-piperidino)-1,2,3,4-tetrahydroisoquinoline derivative **1** was found to exhibit potent and specific bradycardic activities comparable to those of Zatebradine.[10] Linkers between tetrahydroisoquinoline and the piperidine ring of compound **1** were investigated and it was shown that *N*-acyl tetrahydroisoquinoline derivative **2** was equipotent to Zatebradine in vitro and in vivo (Table 1). To probe structure–activity relationships (SAR) around compound **2**, compounds described by formula **I** were prepared and their biological activities evaluated (Fig. 2). Here, the results of a SAR study on a series of *N*-acyl tetrahydroisoquinoline derivatives are reported. The bradycardic activity in conscious rats is also described, subsequent to oral administration of selected compounds.

Keywords: Cardiac disease; Myocardial ischemia; Bradycardic agent; Zatebradine.
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2. Chemistry

Preparation of *N*-acyl tetrahydroisoquinoline derivatives is outlined in Schemes 1–7. Condensation of **3**[11] with 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (**4**) followed by deprotection of benzyl group, provided amine **5**. Compounds **8a–m** were accessed by alkylation of **5** with 3-aryloxypropyl bromides **7a–m**[12] respectively, obtained from the corresponding phenols by treatment with excess 1,3-dibromopropane (Scheme 1). Alkylation of ethyl piperidin-3-ylacetate[13] (**9**) with 3-(3,4-methylenedioxyphenyl)propyl bromide (**7a**) followed by hydrolysis, yielded intermediate acid **10**. Condensation of **10** with 6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (**11**) afforded the desired product **12**. Treatment of 3-pyridylacetic acid with the corresponding tetrahydroisoquinoline derivatives **13** and **14** followed by reduction of pyridine ring, provided amines **15** and **16**, respectively. Alkylation of **15** and **16** with **7a** afforded **17** and **18**, respectively (Scheme 2). 3-Arylalkyl bromides **19**, **20** and **21** were prepared in an analogous manner to **7a**, except that 1,3-dibromopropane was replaced with 1,2-dibromoethane, 1,4-dibromobutane and 1,5-dibromopentane respectively. Compounds **22**, **23** and **24** were obtained by alkylation of **5** with corresponding 3-aryloxyalkyl bromides **19**, **20** and **21** respectively (Scheme 3). Alkylation of **26** (obtained by condensation of **25**[14] with **4** followed by deprotection of BOC group) with **7a** furnished the desired compound **2** (Scheme 4). Condensation of **4** with **27**,[15] followed by reduction of pyridine ring and double bond, gave **29**. Alkylation of **29** with **7a** afforded the desired compound **30** (Scheme 5). 1-Benzylpiperidin-3-amine[16] (**31**) was reacted with 4-nitrophenyl chloroformate followed by treatment with **4** to provide urea **32**. Deprotection of benzyl group followed by alkylation with **7a** provided compound **34** (Scheme 6). Acylation of **4** with methyl chloroformate followed by treatment with **37** (obtained by alkylation of 3-hydroxypiperidine (**36**) with **7a**) provided carbamate **38** (Scheme 7).

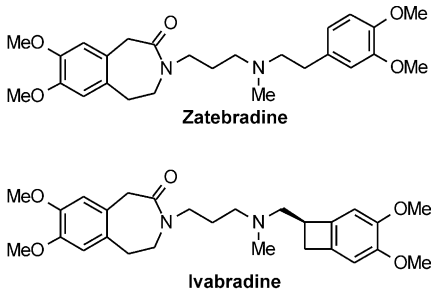


Figure 1.

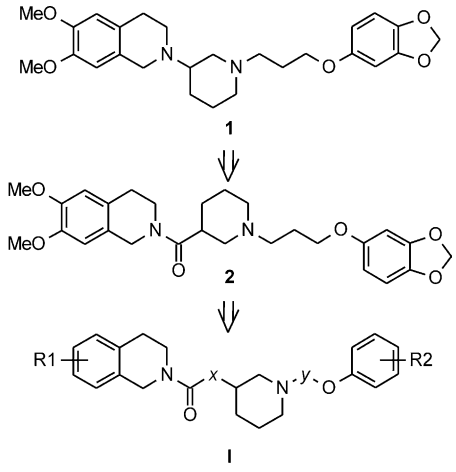
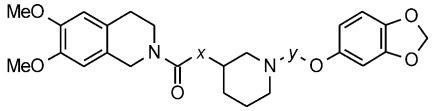


Figure 2.

3. Result and discussion

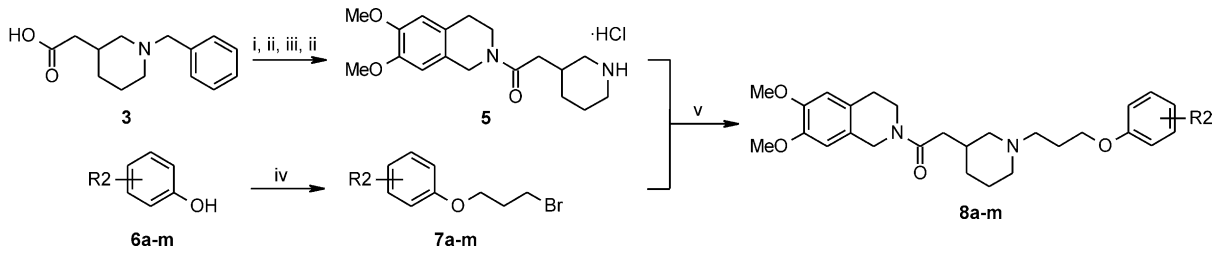
Evaluation of the bradycardic activity exhibited by the synthesized compounds was performed in isolated

Table 1. Bradycardic activities of *N*-acyl-1,2,3,4-tetrahydroisoquinoline derivatives **2**, **8a**, **22–24**, **30**, **34**, **38**

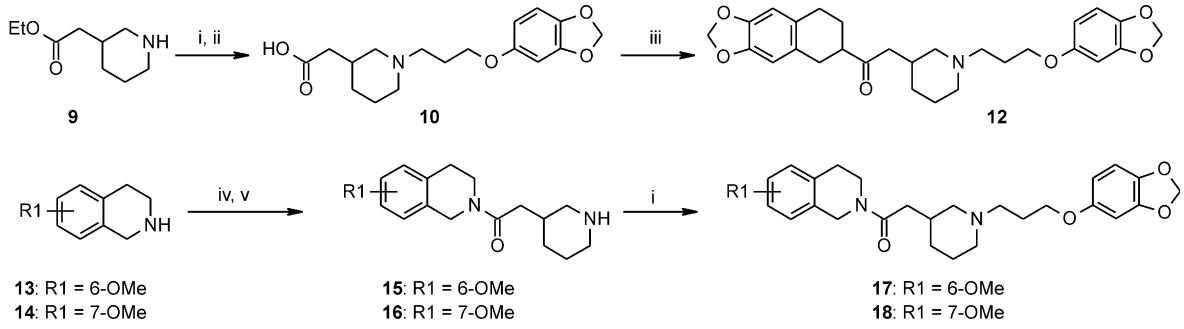


Compd	*x*	*y*	EC_{30}, μM[a]	Anesthetized rats % change[b] at 3 mg/kg iv	
				HR	MBP
1			0.39	−40	−10
2	Bond	$-(CH_2)_3-$	0.37±0.02 (3)	−52±5.4 (3)	−2.5±3.0 (3)
8a	$-CH_2-$	$-(CH_2)_3-$	0.070±0.01 (3)	−48±3.6 (3)	−2.7±4.8 (3)
30	$-(CH_2)_2-$	$-(CH_2)_3-$	0.20	−31	−5.3
34	–NH–	$-(CH_2)_3-$	0.89	NT[c]	NT[c]
38	O	$-(CH_2)_3-$	0.74	NT[c]	NT[c]
22	$-CH_2-$	$-(CH_2)_2-$	0.13	−54	−8.6
23	$-CH_2-$	$-(CH_2)_4-$	0.13	−43	−16
24	$-CH_2-$	$-(CH_2)_5-$	0.31	−35[d]	−18[d]
Zatebradine			0.26±0.05 (7)	−57±2.7 (5)	−1.9±2.4 (5)

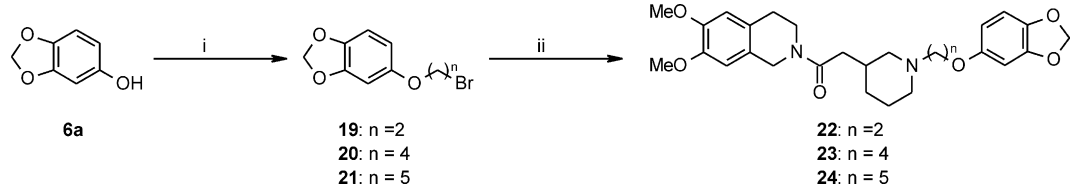
[a] EC_{30} is the concentration required to produce a 30% reduction from the initial beat rates in isolated guinea pigs' right atria. EC_{30} values are shown with±SE (number of determinations) where more than three determination were made. Otherwise results based on two determinations are given.
[b] Percent change from the initial value in urethane-anesthetized rats. Results are shown ±SE (number of determinations) where more than three determinations were made. Otherwise results based on single or two determinations are given.
[c] Not tested.
[d] Results of one experiment.



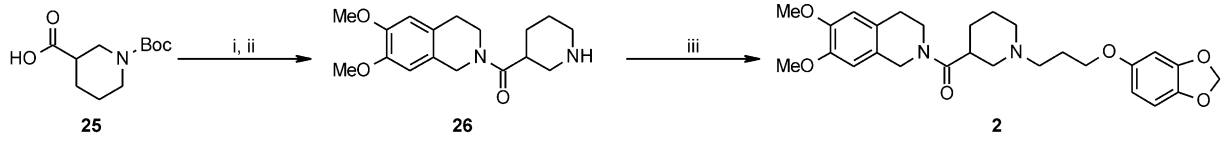
Scheme 1. Synthesis of compounds **8a–m**. Reagents and conditions: (i) 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (**4**), WSC·HCl, HOBt, Et_3N, DMF, THF; (ii) 4 M HCl/AcOEt; (iii) H_2, 20% $Pd(OH)_2/C$, AcOH; (iv) $Br(CH_2)_3Br$, K_2CO_3, CH_3CN, 80 °C; (v) K_2CO_3, CH_3CN, 80 °C.



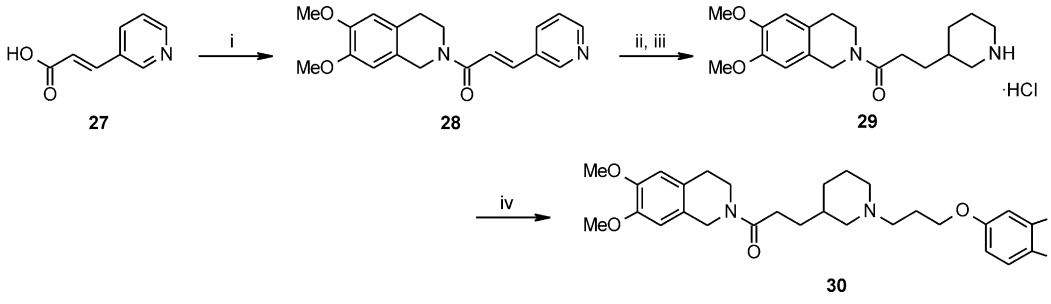
Scheme 2. Synthesis of compounds **12**, **17** and **18**. Reagents and conditions: (i) 3-(3.4-methylenedioxyphenoxy)propyl bromide (**7a**), K_2CO_3, CH_3CN, 80 °C; (ii)NaOH (aq), EtOH; (iii) 6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (**11**), WSC·HCl, HOBt, 1,2-dichloroethane; (iv) 3-pyridylacetic acid hydrochloride, WSC·HCl, HOBt, Et_3N, 1,2-dichloroethane; (v) H_2, PtO_2, AcOH.



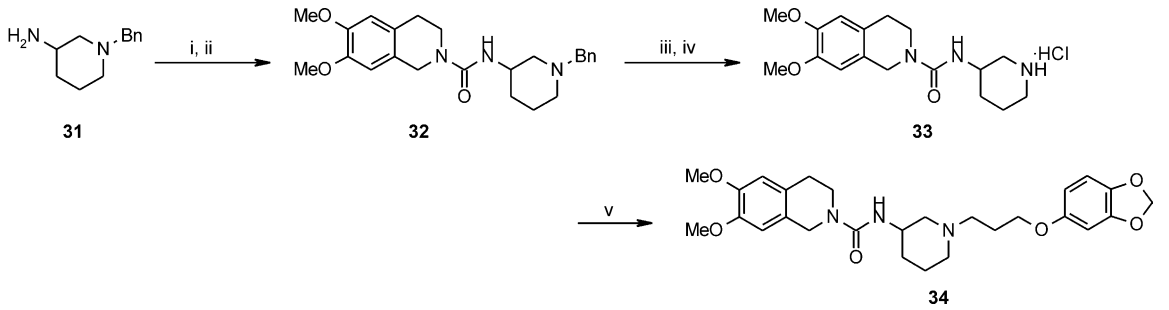
Scheme 3. Synthesis of compounds **22–24**. Reagents and conditions: (i) $Br(CH_2)_nBr$, K_2CO_3, CH_3CN, 80 °C; (ii) **5**, K_2CO_3, CH_3CN, 80 °C.



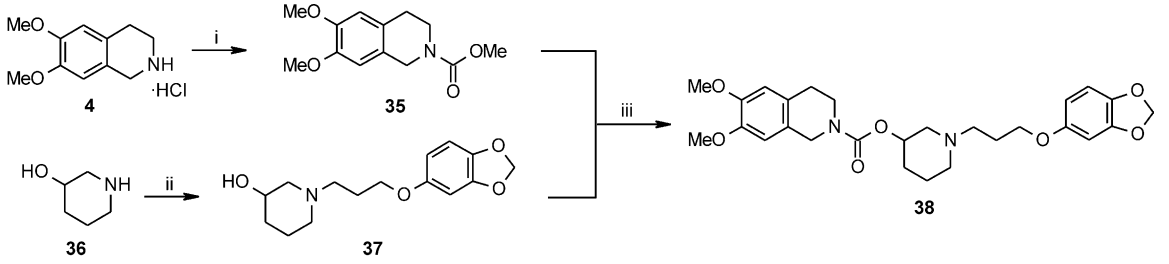
Scheme 4. Synthesis of compound **2**. Reagents and conditions: (i) **4**, WSC·HCl, HOBt, DMF; (ii) 4 M HCl/AcOEt; (iii) **7a**, K_2CO_3, CH_3CN, 80 °C.



Scheme 5. Synthesis of compound **30**. Reagents and conditions: (i) **4**, WSC·HCl, HOBt, THF; (ii) H_2, PtO_2, AcOH; (iii) 4 M HCl/AcOEt; (iv) **7a**, K_2CO_3, CH_3CN, 80 °C.



Scheme 6. Synthesis of compound **34**. Reagents and conditions: (i) 4-nitrophenyl chloroformate, Et_3N, THF; (ii) **4**, Et_3N, DMF, 60 °C; (iii) H_2, 10% Pd/C, AcOH; (iv) 4 M HCl/AcOEt; (v) **7a**, K_2CO_3, CH_3CN, 80 °C.



Scheme 7. Synthesis of compound **38**. Reagents and conditions: (i) $ClCO_2CH_3$, Et_3N, THF; (ii) **7a**, K_2CO_3, CH_3CN, 80 °C; (iii) NaH, toluene, reflux.

guinea pigs right atria in vitro. An EC_{30} value, defined as the concentration of the compound that produces a 30% reduction in the initial spontaneous beating rate, was determined by linear regression. Compounds with high in vitro activities were examined for their effect on HR in urethane-anesthetized rats subsequent to intervenous administration, or conscious rats following oral administration.

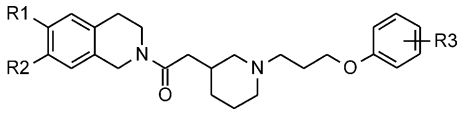
Parent compound **2** exhibited potent bradycardic activity comparable to Zatebradine, with minimal influence on mean blood pressure (MBP). Encouraged by these results, further SAR studies around **2** were conducted in order to establish the effect of the linkers, between the piperidine C-3 position and carbonyl moiety (*x* linker) and between the piperidine nitrogen atom and the oxygen atom (*y* linker).

Insertion of methylene moiety into *x* linker (**8a**) conferred a 5-fold improvement in bradycardic activity in vitro, with an EC_{30} value of 0.07 ± 0.01 μM. Additionally, compound **8a** showed potent bradycardic activity with minimal influence on MBP in vivo. The analogue that possessed a two carbon *x* linker (**30**) was somewhat less active compared to **2**, in in vivo studies. Replacement of the methylene linker of **8a** with nitrogen (**34**) or oxygen (**38**), resulted in a 10-fold loss of in vitro activity. Among the analogues that contain three-carbon *y* linkers, those containing zero- or one-carbon *x* linkers were identified as optimal for specific bradycardic activity (**2** and **8a**). Although shortening (**22**) or extension (**23** and **24**) of the *y* linker alkyl chain was tolerated in terms of in vitro and in vivo bradycardic activities, these compounds affected blood pressure more significantly than **8a**. These results indicated that the optimal composition of the *y* linker is a propyl chain.

The influence of the aryl substituents R1 and R2 on biological activity of **8a** was also evaluated in this study (Table 2). Although bridging the 6,7-positions with methylenedioxy moiety (**12**) did not influence in vitro activity, in vivo bradycardic activity of **12** was less potent than that of **8a**. Removal of the methoxy group from the 6- (**18**) or 7-position (**17**) on 1,2,3,4-tetrahydroisoquinoline was well tolerated in vitro and in vivo. These derivatives, however, showed a relative increase in hypotensive effect, compared to **8a**. These results indicated that 6,7-dimethoxy groups on 1,2,3,4-tetrahydroisoquinoline ring are necessary to confer specific bradycardic activity.

The effect of the aryl substituent R3 on biological activity was subsequently studied (Table 2). Although exchange of 3,4-methylenedioxy group into 3,4-dimethoxy group (**8b**) was well tolerated with regard to in vitro activity, this modification resulted in an increase in hypotensive activity. Furthermore, the effects of monosubstituent on bradycardic and hypotensive activity was examined by introduction of methoxy (**8c–e**) and chloro (**8f–h**) groups. Compounds **8c–g** exhibited a marked hypotensive activity in spite of their potent bradycardic effects. On the other hand, 4-chlorophenyl derivative **8h** was demonstrated to show moderate bradycardic activity with negligible influence on MBP. This finding prompted investigation into the effect of alternative substituents in the *para*-position. Introduction of the fluoro (**8i**) and methyl (**8e**) substituents were well tolerated in the level of in vitro activity. However, these compounds also exhibited comparable hypotensive activity to methoxy derivative **8c**. A series of 4-substituted derivatives bearing electron-withdrawing groups, such as the cyano (**8l**) and trifluoromethyl (**8m**) groups, displayed negligible hypotensive activity and in addition to

Table 2. Bradycardic activities of *N*-acyl-1,2,3,4-tetrahydroisoquinoline derivatives **8a–m 15–17**



Compd	R1	R2	R3	EC_{30}, μM[a]	Anesthetized rats % change[b] at 3 mg/kg iv	
					HR	MBP
8a	OMe	OMe	3,4-OCH_2O–	0.070±0.01 (3)	−48±3.6 (3)	−2.7±4.8 (3)
12	–OCH_2O–		3,4-OCH_2O–	0.17	−17	−17
17	OMe	H	3,4-OCH_2O–	0.18	−40	−17
18	H	OMe	3,4-OCH_2O–	0.13	−46	−20
8b	OMe	OMe	3,4-diOMe	0.20	−43	−12
8c	OMe	OMe	2-OMe	0.16	−60	−28
8d	OMe	OMe	3-OMe	0.20	−48±4.2 (3)	−22±5.2 (3)
8e	OMe	OMe	4-OMe	0.16	−49	−19
8f	OMe	OMe	2-Cl	0.16	−52	−29
8g	OMe	OMe	3-Cl	0.18	−52	−17
8h	OMe	OMe	4-Cl	0.24	−39[d]	2.0[d]
8i	OMe	OMe	4-F	0.13	−50	−30
8j	OMe	OMe	4-Me	0.29	−41[d]	−20[d]
8k	OMe	OMe	4-NO_2	0.19	−30	−9.4
8l	OMe	OMe	4-CN	0.18±0.02 (3)	−45±4.2 (3)	−4.5±3.3 (3)
8m	OMe	OMe	4-CF_3	0.50	−30±2.4 (3)	−7.4±6.1 (3)
Zatebradine				0.26±0.05 (7)	−57±2.7 (5)	1.9±2.4 (5)

[a,b,c,d] See footnote in Table 1.

this, **8l** exhibited potent bradycardic activity comparable to that of **8a** in vivo. As a result of these experiments, the 3,4-methylenedioxy and 4-cyano substituents were identified as optimal for specific bradycardic activity. These observations indicate that the substituent of benzene and their position on the ring are critical in the achievement of specific bradycardic activity.

On the basis of the potent and specific bradycardic activity displayed in isolated guinea pig right atria and in urethane-anesthetized rats, **8a** and **8l** were submitted for further pharmacological evaluation. Compounds **8a** and **8l** (10 mg/kg) were administrated orally to conscious rats and the effect on HR and MBP were examined (Fig. 3). Compound **8a** reduced spontaneous HR up to −106±14.3 beats/min, with negligible influence on MBP (−12.3±5.86 mmHg), and this bradycardic effect was sustained for more than 6 h. In this experiment, **8a** showed increased potency and duration of action compared to those of Zatebradine. Although **8l** was equipotent to **8a** after intravenous administration, **8l** was found to show weaker bradycardic activity and shorter duration of action subsequent to oral administration. Compound **8l** reduced spontaneous HR up to −56.3±15.9 beats/min and its bradycardic effect was sustained for less than 2 h. These results probably indicate that **8a** is better absorbed and has an increase metabolic stability when compared to **8l**.

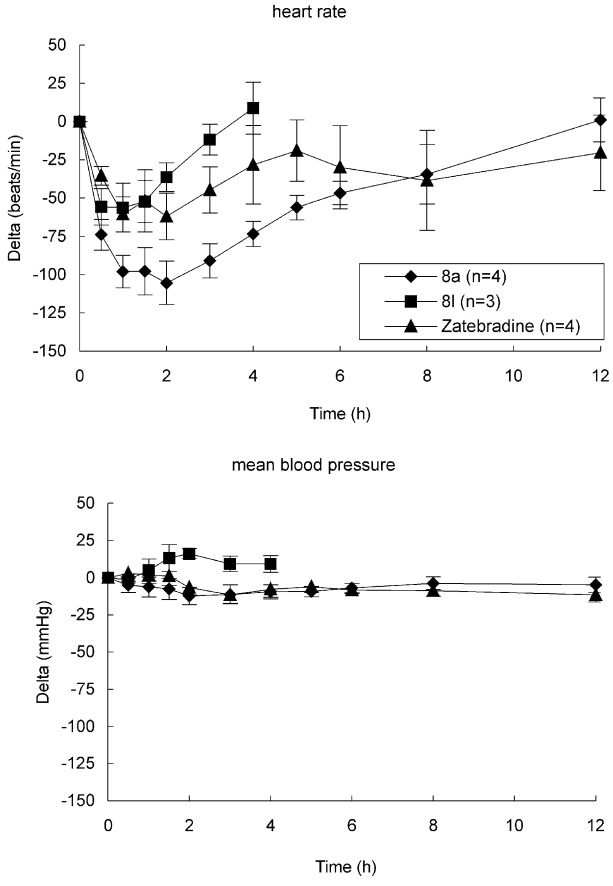


Figure 3. Effects of **8a**, **8l** and Zatebradine on heart rate and mean blood pressure in consious rats. Compounds were orally administrated at time zero. Each point represents mean±SEM from three to four experiments.

4. Conclusions

A series of *N*-acyl-1,2,3,4-tetrahydroisoquinoline derivatives were synthesized and evaluated. SAR studies

within this novel class of compounds revealed that aromatic ring substituents and their position in the ring are critical to the specific induction of bradycardic activity. In this series, compounds **8a** and **8l** show potent and highly specific bradycardic activity subsequent to intravenous administration. Compound **8a** also shows potent and specific bradycardic activity in conscious rats following oral administration. Therefore, compound **8a** may be regarded as a novel lead in pursuit of specific bradycardic agents, on the basis of its pharmacological properties.

5. Experimental

5.1. Chemistry

In general, reagents and solvents were used as purchased without further purification. Melting points were determined with a Yanaco MP-500D melting point apparatus and left uncorrected. ^{1}H NMR spectra were recorded on a JEOL JNM-LA300 or a JEOL JNM-EX400 spectrometer. Chemical shifts were 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. The elemental analyses were performed with a Yanaco MT-5 microanalyzer (C, H, N) and Yokogawa IC-7000S ion chromatographic analyzer (halogens) and were within ±0.4% of theoretical values.

5.1.1. (±)-6,7-Dimethoxy-2-[(piperidin-3-yl)acetyl]-1,2,3,4-tetrahydroisoquinoline hydrochloride (5). To a solution of **4** (1.91 g, 8.33 mmol) in THF (30.0 mL) was added Et_3N (1.16 mL, 8.33 mmol), and the mixture was stirred at room temperature for 10 min. After cooling at 0 °C, to the reaction mixture were added solution of **3** (8.33 mmol) in THF (10.0 mL) and DMF (5.00 mL), HOBt (0.563 g, 4.17 mmol) and WSC·HCl (1.76 g, 9.16 mmol), and the mixture was stirred at room temperature for 9 h. The mixture was partitioned between AcOEt and H_2O, and the organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 98/2–96/4) to give 2-[(1-benzylpiperidin-3-yl) acetyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (4.51 g) as colorless syrup. To a solution of compound obtained above in MeOH (50.0 mL) was added 4 M HCl (g)/AcOEt (2.49 mL, 9.96 mmol), and the mixture was concentrated in vacuo. To a solution of the residual solid in AcOH (30.0 mL) was added $Pd(OH)_2$/C (20 w/w%, 0.185 g), and the mixture was stirred under hydrogen pressure (3.2 kg/cm^2) at room temperature for 15.5 h. The catalyst was filtrated on Celite and the filtrate was concentrated in vacuo. The residue was alkalined with 1 M NaOH (aq), then partitioned between $CHCl_3$ and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo to give the free base of **5** as colorless syrup. This material was converted to its hydrochloride salt by treating with 4 M HCl (g)/AcOEt (2.49 mL, 9.96 mmol). The crude salt was recrystallized from AcOEt–MeOH to give **5** (2.29 g, 78%) as a colorless powder. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.20–1.25 (m, 1H), 1.63–1.80 (m, 3H), 2.20 (brs, 1H), 2.38–2.44 (m, 2H), 2.48–2.80 (m, 4H), 3.15–3.29 (m, 2H), 3.60–3.68 (m, 2H), 3.72 (s, 6H), 4.54 (d, J = 7.5 Hz, 2H), 6.73–6.81 (m, 3H); MS (FAB) m/z = 319 $(M+H)^+$. Anal. calcd for $C_{18}H_{26}N_2O_3$·HCl: C, 60.92; H, 7.67; N, 7.89; Cl, 9.99. Found: C, 60.69; H, 7.64; N, 7.83; Cl, 10.02.

5.1.2. 3-(Aryloxy)propyl bromide (7a–m): General procedure. The synthesis of 3-(3,4-methylenedioxyphenoxy)-propyl bromide (**7a**) 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 cooling at room temperature, the mixture was concentrated in vacuo. The residue was taken with $CHCl_3$ and the $CHCl_3$ layer was washed with 0.2 M NaOH (aq), dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/AcOEt = 9/1) to give **7a** (9.61 g, 74%) as colorless solid. ^{1}H NMR (90 MHz, $CDCl_3$) δ: 2.14–2.41 (m, 2H), 3.59 (t, J = 6.4 Hz, 2H), 4.03 (t, J = 5.9 Hz, 2H), 5.91 (s, 2H), 6.32 (dd, J = 8.4, 2.4 Hz, 1H), 6.50 (d, J = 2.4 Hz, 1H), 6.70 (d, J = 8.4 Hz, 1H); MS (FAB) m/z = 259, 261 $(M+H)^+$.

5.1.3. (±)-6,7-Dimethoxy-2-({1-[3-(3,4-methylenedioxyphenoxy)propyl]-3-piperidyl}acetyl)-1,2,3,4-tetrahydroisoquinoline monooxalate (8a). To a solution of **5** (248 mg, 0.700 mmol) in CH_3CN (6.00 mL) were added K_2CO_3 (203 mg, 1.47 mmol) and **7a** (190 mg, 0.735 mmol), and the mixture was stirred at 80 °C for 6 h. After cooling at room temperature, the mixture was concentrated in vacuo. The residue was partitioned between $CHCl_3$ and H_2O, then the organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 98/2–96/4) to give the free base of **8a** (348 mg, 100%) as a light yellow form. The free base of **8a** was dissolved in MeOH (6.00 mL) and was added oxalic acid (57 mg, 0.63 mmol), and the mixture was concentrated in vacuo. The crude salt was recrystallized from AcOEt–CH_3CN to give **8a** (296 mg, 72%) as colorless powder. mp: 172–173 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.18 (brs, 1H), 1.71–1.80 (m, 3H), 2.05 (brs, 2H), 2.25 (brs, 2H), 2.35–2.41 (m, 2H), 2.61–2.68 (m, 2H), 2.76 (brs, 2H), 3.10 (brs, 2H), 3.39 (brs, 2H), 3.61–3.65 (m, 2H), 3.72 (s, 6H), 3.95 (brs, 2H), 4.54 (d, J = 8.0 Hz, 2H), 5.95 (s, 2H), 6.37 (dd, J = 8.8, 2.4 Hz, 1H), 6.63 (d, J = 2.4 Hz, 1H), 6.74–6.82 (m, 3H); MS (FAB) m/z = 497 $(M+H)^+$. Anal. calcd for $C_{28}H_{36}N_2O_6$·$C_2H_2O_4$·0.1H_2O: C, 61.23; H, 6.54; N, 4.76. Found: C, 61.09; H, 6.26; N, 4.77.

5.1.4. (±)-2-({1-[3-(3,4-Dimethoxyphenoxy)propyl]-3-piperidyl}acetyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline monooxalate (8b). Compound **8b** was prepared from **5** and **7b** in a manner similar to that described for compound **8a** with a yield of 73%. mp: 124–125 °C (AcOEt–CH_3CN); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.16–1.18 (m, 1H), 1.73–1.80 (m, 3H), 2.07 (brs, 2H), 2.26 (brs, 1H), 2.36–2.45 (m, 2H), 2.62–2.68 (m, 2H),

2.74–2.77 (m, 2H), 3.10–3.12 (m, 2H), 3.40 (brs, 2H), 3.61–3.64 (m, 2H), 3.68 (s, 3H), 3.71–3.73 (m, 9H), 3.96–3.97 (m, 2H), 4.54 (d, $J=9.6$ Hz, 2H), 6.42 (dd, $J=8.8$, 2.8 Hz, 1H), 6.56 (d, $J=2.8$ Hz, 1H), 6.74–6.78 (m, 2H), 6.84 (d, $J=8.8$ Hz, 1H); MS (FAB) $m/z=513$ $(M+H)^+$. Anal. calcd for $C_{29}H_{40}N_2O_6\cdot C_2H_2O_4$: C, 61.78; H, 7.02; N, 4.65. Found: C, 61.60; H, 7.03; N, 4.65.

5.1.5. (±)-6,7-Dimethoxy-2-({1-[3-(2-methoxyphenoxy)-propyl]-3-piperidyl}acetyl)-1,2,3,4-tetrahydroisoquinoline monooxalate (8c). Compound **8c** was prepared from **5** and **7c** in a manner similar to that described for compound **8a** with a yield of 75%. mp: 102–105 °C (AcOEt–CH_3CN); ^1H NMR (400 MHz, DMSO-d_6) δ: 1.16–1.19 (m, 1H), 1.68–1.80 (m, 3H), 2.08–2.12 (m, 2H), 2.25 (brs, 1H), 2.41–2.47 (m, 2H), 2.61–2.68 (m, 2H), 2.76 (t, $J=5.6$ Hz, 2H), 3.13 (brs, 2H), 3.39 (brs, 2H), 3.41 (brs, 2H), 3.61–3.67 (m, 2H), 3.71 (s, 6H), 3.75 (s, 3H), 4.00–4.02 (m, 2H), 4.54 (d, $J=8.4$ Hz, 2H), 6.74 (s, 1H), 6.78 (d, $J=4.4$ Hz, 1H), 6.87 (dd, $J=7.6$, 2.0 Hz, 1H), 6.90 (m, 3H), 6.90 (t, $J=2.0$ Hz, 1H), 6.93 (dd, $J=7.2$, 2.0 Hz, 1H), 6.97 (dt, $J=7.6$, 2.0 Hz, 1H); MS (FAB) $m/z=483$ $(M+H)^+$. Anal. calcd for $C_{28}H_{38}N_2O_5\cdot C_2H_2O_4\cdot 0.6H_2O$: C, 61.76; H, 7.12; N, 4.80. Found: C, 61.67; H, 6.99; N, 4.80.

5.1.6. (±)-6,7-Dimethoxy-2-({1-[3-(3-methoxyphenoxy)-propyl]-3-piperidyl}acetyl)-1,2,3,4-tetrahydroisoquinoline monooxalate (8d). Compound **8d** was prepared from **5** and **7d** in a manner similar to that described for compound **8a** with a yield of 64%. mp: 88–93 °C (AcOEt–CH_3CN); ^1H NMR (400 MHz, DMSO-d_6) δ: 1.16–1.19 (m, 1H), 1.68–1.80 (m, 3H), 2.08 (brs, 2H), 2.25 (brs, 1H), 2.39–2.47 (m, 2H), 2.61–2.68 (m, 2H), 2.76 (t, $J=6.0$ Hz, 2H), 3.10–3.12 (m, 2H), 3.40 (brs, 2H), 3.61–3.67 (m, 2H), 3.71 (s, 6H), 3.73 (s, 3H), 4.00–4.03 (m, 2H), 4.54 (d, $J=8.0$ Hz, 2H), 6.48 (t, $J=2.4$ Hz, 1H), 6.51–6.54 (m, 2H), 6.74 (s, 1H), 6.78 (d, $J=3.2$ Hz, 1H), 7.18 (t, $J=8.4$ Hz, 1H); MS (FAB) $m/z=483$ $(M+H)^+$. Anal. calcd for $C_{28}H_{38}N_2O_5\cdot C_2H_2O_4\cdot 0.8H_2O$: C, 61.38; H, 7.14; N, 4.77. Found: C, 61.38; H, 7.15; N, 4.69.

5.1.7. (±)-6,7-Dimethoxy-2-({1-[3-(4-methoxyphenoxy)-propyl]-3-piperidyl}acetyl)-1,2,3,4-tetrahydroisoquinoline monooxalate (8e). Compound **8e** was prepared from **5** and **7e** in a manner similar to that described for compound **8a** with a yield of 76%. mp: 132–136 °C (AcOEt–CH_3CN); ^1H NMR (400 MHz, DMSO-d_6) δ: 1.16–1.18 (m, 1H), 1.67–1.80 (m, 3H), 2.06–2.08 (m, 2H), 2.24 (brs, 1H), 2.39–2.43 (m, 2H), 2.60–2.68 (m, 2H), 2.76 (t, $J=5.6$ Hz, 2H), 3.09–3.11 (m, 2H), 3.40 (brs, 2H), 3.61–3.65 (m, 2H), 3.69 (s, 3H), 3.71 (s, 6H), 3.95–3.98 (m, 2H), 4.54 (d, $J=8.0$ Hz, 2H), 6.74 (s, 1H), 6.78 (d, $J=3.6$ Hz, 1H), 6.86 (s, 4H); MS (FAB) $m/z=483$ $(M+H)^+$. Anal. calcd for $C_{28}H_{38}N_2O_5\cdot C_2H_2O_4\cdot 0.8H_2O$: C, 61.38; H, 7.14; N, 4.77. Found: C, 61.35; H, 7.05; N, 4.67.

5.1.8. (±)-2-({1-[3-(2-Chlorophenoxy)propyl]-3-piperidyl}acetyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline monooxalate (8f). Compound **8f** was prepared from **5** and **7f** in a manner similar to that described for compound **8a** with a yield of 48%. mp: 156–158 °C (AcOEt–CH_3CN); ^1H NMR (400 MHz, DMSO-d_6) δ: 1.16–1.19 (m, 1H), 1.68–1.80 (m, 3H), 2.11–2.16 (m, 2H), 2.25 (brs, 1H), 2.40–2.42 (m, 2H), 2.60–2.68 (m, 2H), 2.76 (t, $J=5.8$ Hz, 2H), 3.12–3.14 (m, 2H), 3.40 (brs, 2H), 3.61–3.67 (m, 2H), 3.71 (s, 6H), 4.11–4.14 (m, 2H), 4.54 (d, $J=8.3$ Hz, 2H), 6.74 (s, 1H), 6.78 (d, $J=3.6$ Hz, 1H), 6.97 (dt, $J=7.6$, 1.1 Hz, 1H), 7.15 (dd, $J=1.0$ Hz, 1H), 7.33 (dt, $J=7.8$, 1.5 Hz, 1H), 7.40–7.45 (dd, $J=7.8$, 1.5 Hz, 1H); MS (FAB) $m/z=487$ $(M+H)^+$. Anal. calcd for $C_{27}H_{35}N_2O_4Cl\cdot C_2H_2O_4\cdot 0.1H_2O$: C, 60.17; H, 6.48; N, 4.84, Cl, 6.12. Found: C, 60.17; H, 6.19; N, 4.84; Cl, 6.03.

5.1.9. (±)-2-({1-[3-(3-Chlorophenoxy)propyl]-3-piperidyl}acetyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline monooxalate hemi hydrate (8g). Compound **8g** was prepared from **5** and **7g** in a manner similar to that described for compound **8a** with a yield of 55%. mp: 90–94 °C (AcOEt–CH_3CN); ^1H NMR (400 MHz, DMSO-d_6) δ: 1.16–1.19 (m, 1H), 1.66–1.80 (m, 3H), 2.08 (brs, 2H), 2.24 (brs, 1H), 2.39–2.43 (m, 2H), 2.59–2.68 (m, 2H), 2.76 (t, $J=5.6$ Hz, 2H), 3.11 (brs, 2H), 3.39 (brs, 2H), 3.61–3.64 (m, 2H), 3.71 (s, 6H), 4.05–4.08 (m, 2H), 4.54 (d, $J=8.3$ Hz, 2H), 6.74 (s, 1H), 6.78 (d, $J=3.9$ Hz, 1H), 6.90–6.94 (m, 1H), 6.98–7.04 (m, 2H), 7.32 (t, $J=8.1$ Hz, 1H); MS (FAB) $m/z=487$ $(M+H)^+$. Anal. calcd for $C_{27}H_{35}N_2O_4Cl\cdot C_2H_2O_4\cdot 0.5H_2O$: C, 59.43; H, 6.54; N, 4.78, Cl, 6.05. Found: C, 59.43; H, 6.18; N, 4.71; Cl, 5.80.

5.1.10. (±)-2-({1-[3-(4-Chlorophenoxy)propyl]-3-piperidyl}acetyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline monooxalate (8h). Compound **8h** was prepared from **5** and **7h** in a manner similar to that described for compound **8a** with a yield of 81%. mp: 117–120 °C (AcOEt–CH_3CN); ^1H NMR (400 MHz, DMSO-d_6) δ: 1.18 (brs, 1H), 1.68–1.79 (m, 3H), 2.08–2.11 (m, 2H), 2.25 (brs, 1H), 2.39–2.43 (m, 2H), 2.60–2.68 (m, 2H), 2.76 (t, $J=5.6$ Hz, 2H), 3.09–3.11 (m, 2H), 3.39 (brs, 2H), 3.61–3.64 (m, 2H), 3.71 (s, 6H), 4.01–4.04 (m, 2H), 4.54 (d, $J=8.4$ Hz, 2H), 6.74 (s, 1H), 6.78 (d, $J=3.6$ Hz, 1H), 6.96 (dt, $J=8.8$, 3.6 Hz, 1H), 7.33 (dt, $J=8.4$, 3.6 Hz, 1H); MS (FAB) $m/z=487$ $(M+H)^+$. Anal. calcd for $C_{27}H_{35}N_2O_4Cl\cdot C_2H_2O_4\cdot 0.5H_2O$: C, 59.43; H, 6.54; N, 4.78, Cl, 6.05. Found: C, 59.33; H, 6.25; N, 4.77; Cl, 6.05.

5.1.11. (±)-2-({1-[3-(4-Fluorophenoxy)propyl]-3-piperidyl}acetyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline monooxalate (8i). Compound **8i** was prepared from **5** and **7i** in a manner similar to that described for compound **8a** with a yield of 81%. mp: 102–106 °C (AcOEt–CH_3CN); ^1H NMR (400 MHz, DMSO-d_6) δ: 1.18 (brs, 1H), 1.67–1.83 (m, 3H), 2.10–2.15 (m, 2H), 3.71 (s, 6H), 3.99–4.00 (m, 2H), 4.54 (d, $J=8.0$ Hz, 2H), 6.74 (s, 1H), 6.78 (d, $J=3.6$ Hz, 1H), 6.92–6.97 (m, 2H), 7.09–7.14 (m, 2H); MS (FAB) $m/z=471$ $(M+H)^+$. Anal. calcd for $C_{27}H_{35}N_2O_4F\cdot C_2H_2O_4\cdot 0.6H_2O$: C, 60.96; H, 6.74; N, 4.90, F, 3.32. Found: C, 60.90; H, 6.61; N, 4.73; F, 3.42.

5.1.12. (±)-6,7-Dimethoxy-2-({1-[3-(4-methylphenoxy)-propyl]-3-piperidyl}acetyl)-1,2,3,4-tetrahydroisoquinoline monooxalate (8j). Compound **8j** was prepared from **5** and **7j** in a manner similar to that described for

compound **8a** with a yield of 67%. mp: 141–142 °C (AcOEt–CH_3CN); ^1H NMR (400 MHz, DMSO-d_6) δ: 1.16–1.19 (m, 1H), 1.68–1.79 (m, 3H), 2.07–2.10 (m, 2H), 2.22 (s, 3H), 2.26 (brs, 1H), 2.35–2.47 (m, 2H), 2.61–2.68 (m, 2H), 2.74–2.77 (m, 2H), 3.10–3.14 (m, 2H), 3.40 (brs, 2H), 3.61–3.67 (m, 2H), 3.71 (s, 6H), 3.97–4.00 (m, 2H), 4.54 (d, J = 8.4 Hz, 2H), 6.74 (s, 1H), 6.78 (d, J = 3.2 Hz, 1H), 6.82 (d, J = 8.8 Hz, 2H), 7.08 (d, J = 8.8 Hz, 2H); MS (FAB) m/z = 467 $(M+H)^+$. Anal. calcd for $C_{28}H_{38}N_2O_4 \cdot C_2H_2O_4$: C, 64.73; H, 7.24; N, 5.03. Found: C, 64.51; H, 7.13; N, 4.99.

5.1.13. (±)-6,7-Dimethoxy-2-({1-[3-(4-nitrophenoxy)propyl]-3-piperidyl}acetyl)-1,2,3,4-tetrahydroisoquinoline monooxalate hemi hydrate (8k). Compound **8k** was prepared from **5** and **7k** in a manner similar to that described for compound **8a** with a yield of 86%. mp: 119–122 °C (AcOEt–CH_3CN); ^1H NMR (400 MHz, DMSO-d_6) δ: 1.18 (brs, 1H), 1.68–1.80 (m, 3H), 2.12–2.14 (m, 2H), 2.25 (brs, 3H), 2.39–2.43 (m, 2H), 2.59–2.68 (m, 2H), 2.76 (d, J = 5.6 Hz, 2H), 3.10–3.12 (m, 2H), 3.39 (brs, 2H), 3.61–3.64 (m, 2H), 3.71 (s, 6H), 4.19–4.20 (m, 2H), 4.54 (d, J = 9.6 Hz, 2H), 6.74 (s, 1H), 6.78 (d, J = 2.4 Hz, 1H), 7.15 (d, J = 9.2 Hz, 2H), 8.22 (d, J = 9.2 Hz, 2H); MS (FAB) m/z = 498 $(M+H)^+$. Anal. calcd for $C_{27}H_{35}N_3O_6 \cdot C_2H_2O_4 \cdot 0.5H_2O$: C, 58.38; H, 6.42; N, 7.04. Found: C, 58.40; H, 6.43; N, 6.80.

5.1.14. (±)-4-(3-{3-[2-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolyl)-2-oxoethyl]-1-piperidyl}propoxy)benzonitrile monooxalate (8l). Compound **8l** was prepared from **5** and **7l** in a manner similar to that described for compound **8a** with a yield of 75%. mp: 120–123 °C (AcOEt–CH_3CN); ^1H NMR (400 MHz, DMSO-d_6) δ: 1.18 (brs, 1H), 1.70–1.79 (m, 3H), 2.11 (brs, 2H), 2.24 (brs, 1H), 2.39–2.43 (m, 2H), 2.59–2.68 (m, 2H), 2.74–2.77 (m, 2H), 3.11 (brs, 2H), 3.39 (brs, 2H), 3.61–3.64 (m, 2H), 3.71 (s, 6H), 4.14 (brs, 2H), 4.53 (d, J = 8.8 Hz, 2H), 6.74 (s, 1H), 6.78 (d, J = 3.2 Hz, 1H), 7.11 (d, J = 8.8 Hz, 2H), 7.78 (d, J = 8.4 Hz, 2H); MS (FAB) m/z = 478 $(M+H)^+$. Anal. calcd for $C_{28}H_{35}N_3O_4 \cdot C_2H_2O_4 \cdot 0.3H_2O$: C, 62.88; H, 6.61; N, 7.33. Found: C, 62.83; H, 6.65; N, 7.23.

5.1.15. (±)-6,7-Dimethoxy-2-({1-[3-(4-trifluoromethylphenoxy)propyl]-3-piperidyl}acetyl)-1,2,3,4-tetrahydroisoquinoline monooxalate (8m). Compound **8m** was prepared from **5** and **7m** in a manner similar to that described for compound **8a** with a yield of 83%. mp: 86–88 °C (AcOEt); ^1H NMR (400 MHz, DMSO-d_6) δ: 1.18 (brs, 1H), 1.68–1.80 (m, 3H), 2.11–2.14 (m, 2H), 2.25 (brs, 1H), 2.40–2.43 (m, 2H), 2.61–2.68 (m, 2H), 2.76 (t, J = 5.6 Hz, 2H), 3.10–3.12 (m, 2H), 3.40 (brs, 2H), 3.63–3.67 (m, 2H), 3.71 (s, 6H), 4.11–4.14 (m, 2H), 4.54 (d, J = 8.8 Hz, 2H), 6.74 (s, 1H), 6.78 (d, J = 2.8 Hz, 1H), 7.12 (d, J = 8.8 Hz, 2H), 7.66 (d, J = 8.8 Hz, 2H); MS (FAB) m/z = 521 $(M+H)^+$. Anal. calcd for $C_{28}H_{35}N_3O_4F_3 \cdot C_2H_2O_4 \cdot 0.7H_2O$: C, 57.82; H, 6.21; N, 4.49; F, 9.15. Found: C, 57.95; H, 6.10; N, 4.19; F, 9.15.

5.1.16. (±)-{1-[4-(1,3-Benzodioxol-5-yl)butyl]piperidin-3-yl}acetic acid (10). To a solution of **9** (3.00 g, 17.5 mmol) in CH_3CN (30.0 mL) were added K_2CO_3 (2.66 g, 19.3 mmol) and **7a** (5.00 g, 19.3 mmol), and the mixture was stirred at 80 °C for overnight. After cooling at room temperature, the mixture was concentrated in vacuo. The residue was partitioned between $CHCl_3$ and $NaHCO_3$ (aq). The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 100/1–50/1) to give (±)-ethyl {1-[3-(1,3-benzodioxol-5-yloxy)propyl]piperidin-3-yl}acetate (4.23 g, 70%) as yellow oil. To a solution of compound obtained above in EtOH (20.0 mL) was added 1 M NaOH (aq), and the mixture was stirred at room temperature for 1 h. To the reaction mixture was added 1 M HCl (aq) (12.0 mL), and the mixture was concentrated in vacuo. The residue was suspended in EtOH, filtered and concentrated in vacuo to give **10** (4.76 g, quant.) as colorless amorphous. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.04 (brs, 1H), 1.60–2.40 (m, 9H), 2.75 (brs, 2H), 3.05 (brs, 1H), 3.89 (brs, 2H), 5.88 (s, 2H), 6.27 (d, J = 7.8 Hz, 1H), 6.45 (s, 1H), 6.66 (d, J = 8.4 Hz, 1H); MS (FAB) m/z = 322 $(M+H)^+$.

5.1.17. (±)-6,7-Methylenedioxy-2-({1-[3-(3,4-methylenedioxyphenoxy)propyl]-3-piperidyl}acetyl)-1,2,3,4-tetrahydroisoquinoline monooxalate (12). To a solution of **10** (720 mg, 2.24 mmol) and **11** (360 mg, 2.03 mmol) in 1,2-dichloroethane (20.0 mL) were added HOBt (140 mg, 1.02 mmol) and WSC·HCl (430 mg, 2.24 mmol), and the mixture was stirred at room temperature for 6 h. The reaction mixture was alkalized with 1 M NaOH (aq), then extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 100/1–50/1) to give the free base of **12**. To a solution of free base of **12** in MeOH (10.0 mL) was added oxalic acid (160 mg), and the mixture was concentrated in vacuo. The crude salt was recrystallized from AcOEt–EtOH to give **12** (400 mg, 35%) as colorless powder. mp: 130–133 °C (AcOEt–EtOH); ^1H NMR (400 MHz, DMSO-d_6) δ: 1.16–1.19 (m, 1H), 1.65–1.80 (m, 3H), 2.05–2.06 (m, 2H), 2.25 (brs, 1H), 2.34–2.41 (m, 2H), 2.60–2.69 (m, 2H), 2.74 (t, J = 5.4 Hz, 2H), 3.11 (brs, 2H), 3.32–3.48 (m, 2H), 3.56–3.66 (m, 2H), 3.95 (t, J = 5.9 Hz, 2H), 4.50 (d, J = 9.7 Hz, 2H), 5.95 (s, 4H), 6.37 (dd, J = 8.3, 2.4 Hz, 1H), 6.63 (d, J = 2.4 Hz, 2H), 6.73–6.82 (m, 3H); MS (FAB) m/z = 481 $(M+H)^+$. Anal. calcd for $C_{27}H_{34}N_2O_5 \cdot C_2H_2O_4 \cdot 0.1H_2O$: C, 61.04; H, 6.01; N, 4.91. Found: C, 60.92; H, 5.96; N, 4.70.

5.1.18. (±)-6-Methoxy-2-[(piperidin-3-yl)acetyl]-1,2,3,4-tetrahydroisoquinoline (15). To a suspension of **13** (3.18 g, 15.9 mmol) in 1,2-dichloroethane (90.0 mL) were added Et_3N (5.08 mL, 36.6 mmol), 3-pyridylaceticacid hydrochloride (3.32 g, 19.1 mmol), HOBt (1.07 g, 7.95 mmol) and WSC·HCl (3.66 g, 19.1 mmol), and the mixture was stirred at room temperature for overnight. The reaction mixture was alkalized with 1 M NaOH (aq), then extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 100/0–100/1) to give 6-methoxy-2-[(pyridin-3-yl)acetyl]-1,2,3,4-tetrahydroisoquinoline

(3.49 g, 78%). To a solution of compound obtained above in AcOH (35.0 mL) was added PtO_2 (350 mg), and the mixture was stirred under hydrogen pressure (3.0 kg/cm^2) at room temperature for 5 h. The catalyst was removed by filtration on Celite and the filtrate was concentrated in vacuo. The residue was alkalized with 1 M NaOH (aq), then extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH/NH_4OH = 100/1/0–30/1/0.1–20/1/0.1) to give **15** (1.50 g, 42%). as yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.11–1.26 (m, 1H), 1.35–2.40 (m, 6H), 2.50–2.62 (m, 1H), 2.70–2.15 (m, 6H), 3.35 (d, J = 10.2 Hz, 1H), 3.66 (t, J = 6.00 Hz, 1H), 3.62–3.67 (m, 2H), 3.79 (s, 3H), 4.56–4.66 (m, 2H), 6.66–6.72 (m, 1H), 6.76 (dd, J = 8.4, 2.4 Hz, 1H), 7.03 (dd, J = 16.8, 8.4 Hz, 1H); MS (FAB) m/z = 289 $(M+H)^+$.

5.1.19. (±)-7-Methoxy-2-[(piperidin-3-yl)acetyl]-1,2,3,4-tetrahydroisoquinoline hydrochloride (16). Compound **16** was prepared from **14** in a manner similar to that described for compound **15** with a yield of 75%. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.15–1.26 (m, 1H), 1.62–1.74 (m, 3H), 2.20 (brs, 1H), 2.41–2.43 (m, 2H), 2.56–2.70 (m, 2H), 2.78 (t, J = 5.9 Hz, 2H), 3.14–3.25 (m, 2H), 3.62–3.67 (m, 2H), 3.72 (d, J = 3.0 Hz, 2H), 4.60 (d, J = 8.7 Hz, 2H), 6.74–6.78 (m, 2H), 7.08 (d, J = 8.4 Hz, 1H), 8.83 (brs, 1H), 9.13 (brs, 1H); MS (FAB) m/z = 289 $(M+H)^+$. Anal. calcd for $C_{17}H_{24}N_2O_2$·HCl: C, 61.83; H, 7.81; N, 8.48; Cl, 10.73. Found: C, 61.56; H, 7.75; N, 8.47; Cl, 10.91.

5.1.20. (±)-6-Methoxy-2-({1-[3-(3,4-methylenedioxyphenoxy)propyl]-3-piperidyl}acetyl)-1,2,3,4-tetrahydroisoquinoline monooxalate (17). Compound **17** was prepared from **7a** and **15** in a manner similar to that described for compound **8a** with a yield of 38%. mp: 78–81 °C (AcOEt–EtOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.16–1.20 (m, 1H), 1.60–1.85 (m, 3H), 2.03–2.10 (m, 2H), 2.20–2.30 (m, 1H), 2.38–2.45 (m, 2H), 2.50–2.65 (m, 2H), 2.70–2.85 (m, 4H), 3.11 (brs, 2H), 3.40 (brs, 2H), 3.60–3.67 (m, 2H), 3.72 (s, 3H), 3.95 (t, J = 5.9 Hz, 2H), 4.54 (d, J = 12.2 Hz, 2H), 5.95 (s, 2H), 6.37 (dd, J = 8.3, 2.4 Hz, 1H), 6.63 (d, J = 2.4 Hz, 2H), 6.73–6.78 (m, 2H), 6.80 (d, J = 8.3 Hz, 1H), 7.10 (d, J = 8.8 Hz, 1H); MS (FAB) m/z = 467 $(M+H)^+$. Anal. calcd for $C_{27}H_{34}N_2O_5$·$C_2H_2O_4$·0.3H_2O: C, 61.98; H, 6.56; N, 4.98. Found: C, 61.87; H, 6.71; N, 4.88.

5.1.21. (±)-7-Methoxy-2-({1-[3-(3,4-methylenedioxyphenoxy)propyl]-3-piperidyl}acetyl)-1,2,3,4-tetrahydroisoquinoline monooxalate (18). Compound **18** was prepared from **7a** and **16** in a manner similar to that described for compound **8a** with a yield of 63%. mp: 121–123 °C (AcOEt–CH_3CN); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.16–1.18 (m, 1H), 1.67–1.79 (m, 3H), 2.03–2.07 (m, 2H), 2.25 (brs, 1H), 2.40–2.41 (m, 2H), 2.60–2.69 (m, 2H), 2.77 (t, J = 5.9 Hz, 2H), 3.10 (brs, 2H), 3.39 (brs, 2H), 3.62–3.67 (m, 2H), 3.72 (d, J = 2.9 Hz, 3H), 3.95 (t, J = 5.9 Hz, 2H), 4.60 (d, J = 9.7 Hz, 2H), 5.95 (s, 2H), 6.37 (dd, J = 8.8, 2.4 Hz, 1H), 6.63 (d, J = 2.4 Hz, 2H), 6.74–6.78 (m, 2H), 6.81 (d, J = 8.3 Hz, 1H), 7.08 (d, J = 8.3 Hz, 1H); MS (FAB) m/z = 467 $(M+H)^+$. Anal. calcd for $C_{27}H_{34}N_2O_5$·$C_2H_2O_4$·0.1H_2O: C, 62.38; H, 6.53; N, 5.02. Found: C, 62.27; H, 6.62; N, 5.02.

5.1.22. 2-(3,4-Methylenedioxyphenoxy)ethyl bromide (19). Compound **19** was prepared from **6a** and 1,2-dibromoethane in a manner similar to that described for compound **7a** with a yield of 18%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.60 (t, J = 6.0 Hz, 2H), 4.21 (t, J = 6.0 Hz, 2H), 5.92 (s, 2H), 6.34 (dd, J = 8.4, 2.8 Hz, 1H), 6.52 (d, J = 2.4 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H); MS (EI) m/z = 244, 246 $(M)^+$.

5.1.23. 4-(3,4-Methylenedioxyphenoxy)butyl bromide (20). Compound **20** was prepared from **6a** and 1,4-dibromobutane in a manner similar to that described for compound **7a** with a yield of 73%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.86–1.96 (m, 2H), 2.00–2.12 (m, 2H), 3.48 (t, J = 6.8 Hz, 2H), 4.92 (t, J = 6.0 Hz, 2H), 5.91 (s, 2H), 6.30 (dd, J = 8.4, 2.4 Hz, 1H), 6.48 (d, J = 2.8 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H); MS (EI) m/z = 272, 274 $(M)^+$.

5.1.24. 5-(3,4-Methylenedioxyphenoxy)pentyl bromide (21). Compound **21** was prepared from **6a** and 1,5-dibromopentane in a manner similar to that described for compound **7a** with a yield of 92%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.55–1.65 (2H, m), 1.70–1.85 (m, 2H), 1.89–1.96 (m, 2H), 3.43 (t, J = 7.2 Hz, 2H), 3.89 (t, J = 6.4 Hz, 2H), 5.90 (s, 2H), 6.31 (dd, J = 8.6, 2.4 Hz, 1H), 6.48 (d, J = 2.4 Hz, 1H), 6.69 (d, J = 8.4 Hz, 1H); MS (EI) m/z = 286, 288 $(M)^+$.

5.1.25. (±)-6,7-Dimethoxy-2-({1-[3-(3,4-methylenedioxyphenoxy)ethyl]-3-piperidyl}acetyl)-1,2,3,4-tetrahydroisoquinoline monooxalate (22). Compound **22** was prepared from **7a** and **19** in a manner similar to that described for compound **8a** with a yield of 59%. mp: 108–116 °C (AcOEt–CH_3CN); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.13–1.16 (m, 1H), 1.77 (brs, 3H), 2.27 (brs, 1H), 2.34–2.46 (m, 2H), 2.66 (t, J = 6.0 Hz, 2H), 2.75 (t, J = 6.4 Hz, 2H), 3.30–3.44 (m, 4H), 3.64 (dd, J = 12.4, 6.0 Hz, 3H), 3.71 (s, 6H), 4.20–4.21 (m, 2H), 4.53 (d, J = 12.0 Hz, 2H), 5.97 (s, 2H), 6.41 (dt, J = 8.8, 2.8 Hz, 1H), 6.681 (d, J = 2.4 Hz, 1H), 6.74 (s, 1H), 6.77 (d, J = 2.4 Hz, 1H), 6.82 (dd, J = 8.8, 5.2 Hz, 1H); MS (FAB) m/z = 483 $(M+H)^+$. Anal. calcd for $C_{27}H_{34}N_2O_6$·$C_2H_2O_4$·0.4H_2O: C, 60.07; H, 6.40; N, 4.83. Found: C, 60.01; H, 6.68; N, 4.80.

5.1.26. (±)-6,7-Dimethoxy-2-({1-[3-(3,4-methylenedioxyphenoxy)butyl]-3-piperidyl}acetyl)-1,2,3,4-tetrahydroisoquinoline monooxalate 0.1 hydrate (23). Compound **23** was prepared from **7a** and **20** in a manner similar to that described for compound **8a** with a yield of 86%. mp: 159–161 °C (AcOEt–CH_3CN); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.16–1.18 (m, 1H), 1.69–1.79 (m, 7H), 2.25 (brs, 1H), 2.35–2.47 (m, 2H), 2.66 (t, J = 6.0 Hz, 2H), 2.76 (t, J = 6.0 Hz, 2H), 3.02 (brs, 2H), 3.38 (brs, 2H), 3.61–3.66 (m, 2H), 3.71 (s, 6H), 3.90 (t, J = 6.0 Hz, 2H), 4.53 (d, J = 7.2 Hz, 2H), 5.95 (s, 2H), 6.36 (dd, J = 8.4, 2.0 Hz, 1H), 6.62 (d, J = 2.4 Hz, 1H), 6.74 (s, 1H), 6.77 (d, J = 3.6 Hz, 1H), 6.80 (d, J = 8.0 Hz, 1H); MS (FAB) m/z = 511 $(M+H)^+$. Anal. calcd for

$C_{29}H_{38}N_2O_6 \cdot C_2H_2O_4 \cdot 0.1H_2O$: C, 61.80; H, 6.73; N, 4.65. Found: C, 61.97; H, 7.03; N, 4.69.

5.1.27. (±)-6,7-Dimethoxy-2-({1-[3-(3,4-methylenedioxyphenoxy)pentyl]-3-piperidyl}acetyl)-1,2,3,4-tetrahydroisoquinoline monooxalate (24). Compound **24** was prepared from **7a** and **21** in a manner similar to that described for compound **8a** with a yield of 73%. mp: 132–140 °C (AcOEt–CH_3CN); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.16 (brs, 1H), 1.39–1.42 (m, 2H), 1.66–1.71 (m, 5H), 1.78 (brs, 2H), 2.25 (brs, 1H), 2.35–2.47 (m, 2H), 2.66 (t, J = 6.0 Hz, 2H), 2.76 (t, J = 6.0 Hz, 2H), 2.96–2.98 (m, 2H), 3.38 (brs, 2H), 3.61–3.65 (m, 2H), 3.72 (s, 6H), 3.88 (t, J = 6.4 Hz, 2H), 4.53 (d, J = 8.0 Hz, 2H), 5.94 (s, 2H), 6.35 (dd, J = 8.4, 2.4 Hz, 1H), 6.60 (d, J = 2.4 Hz, 1H), 6.74 (s, 1H), 6.77 (s, 1H), 6.79 (d, J = 8.4 Hz, 1H); MS (FAB) m/z = 525 $(M+H)^+$. Anal. calcd for $C_{30}H_{40}N_2O_6 \cdot C_2H_2O_4$: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.63; H, 7.42; N, 4.52.

5.1.28. (±)-6,7-Dimethoxy-2-[(piperidin-3-yl)carbonyl]-1,2,3,4-tetrahydroisoquinoline (26). To a suspension of **4** (1.19 g, 5.00 mmol) in 1,2-dichloroethane (30.0 mL) were added Et_3N (0.694 mL, 5.00 mmol), **25** (1.08 g, 5.00 mmol), HOBt (0.340 g, 2.50 mmol) and WSC·HCl (1.15 g, 6.00 mmol), and the mixture was stirred at room temperature for 4 h. The reaction mixture was washed with 5% citric acid (aq), $NaHCO_3$ (aq) and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 100/0–100/1) to give *tert*-butyl 3-[(6,7-dimethoxy-3,4-dihydroisoquinolin-2-(1*H*)-yl)carbonyl]piperidine-1-carboxylate (1.84 g, 91%). To this compound was added 4 M HCl (g)/AcOEt (5.00 mL), and the mixture was stirred at room temperature for 2.5 h. The mixture was concentrated in vacuo. The residue was alkalized with 1 M NaOH (aq), then extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo to give **26** (1.32 g, 95%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.45–1.60 (m, 1H), 1.68–1.80 (m, 2H), 1.90 (brs, 1H), 2.62–2.95 (m, 5H), 2.96–3.12 (m, 2H), 3.68–3.84 (m, 4H), 3.86 (s, 6H), 4.58–4.67 (m, 2H), 6.57–6.65 (m, 2H); MS (FAB) m/z = 305 $(M+H)^+$.

5.1.29. (±)-6,7-Dimethoxy-2-({1-[3-(3,4-methylenedioxyphenoxy)propyl]-3-piperidyl}carbonyl)-1,2,3,4-tetrahydroisoquinoline monohydrochloride (2). Compound **2** was prepared from **7a** and **25** in a manner similar to that described for compound **8a** with a yield of 29%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.18–1.92 (m, 1H), 1.80–1.95 (m, 3H), 2.10–2.20 (m, 2H), 2.65–3.10 (m, 4H), 2.61–2.68 (m, 2H), 3.21 (brs, 2H), 3.35–3.65 (m, 3H), 3.72 (s, 6H), 3.96–3.98 (m, 2H), 4.45–4.70 (m, 2H), 5.96(s, 2H), 6.35–6.42 (m, 1H), 6.62–6.66 (m, 1H), 6.74–6.83 (m, 3H); MS (FAB) m/z = 483 $(M+H)^+$. Anal. calcd for $C_{27}H_{34}N_2O_6 \cdot HCl \cdot 1.2H_2O$: C, 59.98; H, 6.97; N, 5.18; Cl, 6.59. Found: C, 61.09; H, 6.26; N, 4.77; Cl, 6.54.

5.1.30. (±)-6,7-Dimethoxy-2-[(2*E*)-3-pyridin-3-ylprop-2-enoyl]-1,2,3,4-tetrahydroisoquinoline (28). To a solution of **4** (2.05 g, 8.91 mmol) in THF (30.0 mL) was added Et_3N (1.24 mL, 8.91 mmol), and the mixture was stirred at room temperature for 10 min. After cooling at 0 °C, to the reaction mixture were added solution of **27** (1.46 g, 9.80 mmol) in THF (10.0 mL), HOBt (0.602 g, 4.46 mmol) and WSC·HCl (1.88 g, 9.80 mmol), and the mixture was stirred at room temperature for 4.5 h. The mixture was partitioned between AcOEt and H_2O, and the organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 98/2–96/4) to give **28** (2.19 g, 76%) as light yellow syrup. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.80–2.95 (m, 2H), 3.79–3.93 (m, 8H), 4.78 (brs, 2H), 6.59–6.70 (m, 2H), 7.07 (d, J = 15.3 Hz, 1H), 7.32 (dd, J = 8.1, 4.8 Hz, 1H), 7.69 (d, J = 15.3 Hz, 3H), 7.80–7.88 (m, 1H), 8.58 (dd, J = 4.7, 1.5 Hz, 1H), 8.79 (d, J = 1.8 Hz, 1H), 6.681 (d, J = 2.4 Hz, 1H), 6.74 (s, 1H), 6.77 (d, J = 2.4 Hz, 1H), 6.82 (dd, J = 8.8, 5.2 Hz, 1H); MS (FAB) m/z = 325 $(M+H)^+$.

5.1.31. (±)-6,7-Dimethoxy-2-(3-piperidin-3-ylpropanoyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride (29). To a solution of **28** (2.17 g, 6.68 mmol) in AcOH (20.0 mL) was added PtO_2 (217 mg), and the mixture was stirred under hydrogen pressure (3.2 kg/cm^2) at room temperature for 6 h. The catalyst was filtrated on Celite and the filtrate was concentrated in vacuo. The residue was alkalined with 1 M NaOH (aq), then partitioned between $CHCl_3$ and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo to give the free base of **29** as colorless syrup. This material was converted to its hydrochloride salt by treating with 4 M HCl (g)/AcOEt (2.00 mL, 8.02 mmol). The crude salt was recrystallized from AcOEt–EtOH to give **29** (2.21 g, 90%) as light yellow powder. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.02–1.22 (m, 1H), 1.38–1.86 (m, 6H), 2.43 (t, J = 5.9 Hz, 2H), 2.62–2.80 (m, 3H), 3.19 (t, J = 12.9 Hz, 2H), 3.35 (brs, 1H), 3.64 (t, J = 5.9 Hz, 2H), 3.71 (s, 6H), 4.54 (d, J = 16.8 Hz, 2H), 6.74 (s, 1H), 6.78 (s, 1H), 8.76–8.84 (m, 1H), 9.00–9.10 (m, 1H); MS (FAB) m/z = 333 $(M+H)^+$. Anal. calcd for $C_{19}H_{28}N_2O_3 \cdot HCl \cdot 0.5H_2O$: C, 60.39; H, 8.00; N, 7.41; Cl, 9.38. Found: C, 60.33; H, 8.05; N, 7.23; Cl, 9.26.

5.1.32. (±)-6,7-Dimethoxy-2-(3-{1-[3-(3,4-methylenedioxyphenoxy)propyl]-3-piperidyl}propanoyl)-1,2,3,4-tetrahydroisoquinoline monooxalate (30). Compound **29** was prepared from **7a** and **28** in a manner similar to that described for compound **8a** with a yield of 88%. mp: 147–149 °C (AcOEt–CH_3CN); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.06–1.09 (m, 1H), 1.47–1.53 (m, 2H), 1.64–1.67 (m, 1H), 1.79–1.82 (m, 3H), 2.07–2.08 (m, 2H), 2.45 (t, J = 7.2 Hz, 2H), 2.52 (brs, 1H), 2.65 (t, J = 5.6 Hz, 1H), 2.75–2.78 (m, 2H), 3.08–3.09 (m, 2H), 3.39 (brs, 2H), 3.64 (t, J = 6.0 Hz, 2H), 3.71 (s, 3H), 3.72 (s, 3H), 3.95 (t, J = 6.0 Hz, 2H), 4.54 (d, J = 20.8 Hz, 2H), 5.95 (s, 2H), 6.37 (dd, J = 8.8, 2.4 Hz, 1H), 6.62 (d, J = 2.4 Hz, 1H), 6.74 (s, 1H), 6.77 (d, J = 4.0 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H); MS (FAB) m/z = 511 $(M+H)^+$. Anal. calcd for $C_{29}H_{38}N_2O_6 \cdot C_2H_2O_4$: C, 61.99; H, 6.71; N, 4.66. Found: C, 61.76; H, 6.69; N, 4.66.

5.1.33. (±)-*N*-(1-Benzylpiperidin-3-yl)-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1*H*)-carboxamide (32). To a

solution of **31** (0.951 g, 5.00 mmol) and Et_3N (0.836 mL, 6.00 mmol) in THF (15.0 mL) was added 4-nitrophenyl chloroformate (1.11 g, 5.50 mmol) at 0 °C, and the mixture was stirred at room temperature for 40 min. The mixture was partitioned between AcOEt and H_2O. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo to give 4-nitrophenyl(1-benzylpiperidin-3-yl)carbamate as yellow syrup. To the solution of compound obtained above in DMF (20.0 mL) were added Et_3N (1.39 mL, 10.0 mmol) and free base of **4** (1.16 g, 6.00 mmol), and the mixture was stirred at 60 °C for 18 h. After cooling at 0 °C, the mixture was partitioned between AcOEt and H_2O. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 99/12–98/2) to give **32** (2.12 g, 100%) as yellow syrup. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.54–1.67 (m, 4H), 2.20–2.64 (m, 3H), 2.80 (t, J = 6.0 Hz, 2H), 2.85–2.97 (m, 1H), 3.46–3.65 (m, 4H), 3.87 (s, 6H), 4.02 (brs, 1H), 4.46 (s, 2H), 6.65 (d, J = 3.0 Hz, 2H), 7.24–7.33 (m, 5H); MS (FAB) m/z = 410 $(M+H)^+$.

5.1.34. (±)-6,7-Dimethoxy-*N*-piperidin-3-yl-3,4-dihydroisoquinoline-2(1*H*)-carboxamide hydrochloride (33). To a solution of **32** (2.10 g, 4.90 mmol) in MeOH (20.0 mL) was added 4 M HCl (g) / AcOEt (1.47 mL, 5.88 mmol), and the mixture was concentrated in vacuo. To a solution of the residual solid in AcOH (20.0 mL) was added Pd/C (10 w/w%, 109 mg), and the mixture was stirred under hydrogen pressure (3.2 kg/cm^2) at 70 °C for 24 h. The catalyst was filtrated on Celite and the filtrate was concentrated in vacuo. The residue was alkalined with 1 M NaOH (aq), then partitioned between $CHCl_3$ and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo to give the free base of **33** as a light yellow syrup. This material was converted to its hydrochloride salt by treating with 4 M HCl (g)/AcOEt (1.47 mL, 5.88 mmol). The crude salt was recrystallized from Et_2O–EtOH to give **32** (1.35 g, 77%) as pale yellow powder. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.54–1.60 (m, 1H), 1.67–1.82 (m, 3H), 2.66 (t, J = 5.4 Hz, 2H), 2.85–2.97 (m, 2H), 3.03–3.20 (m, 2H), 3.33 (brs, 1H), 3.54 (t, J = 6.0 Hz, 2H), 3.70 (s, 6H), 3.88 (brs, 1H), 4.41 (s, 2H), 6.62 (d, J = 7.5 Hz, 1H), 6.69 (d, J = 9.6 Hz, 1H), 8.88 (brs, 1H), 9.22 (brs, 1H); MS (FAB) m/z = 320 $(M+H)^+$.

5.1.35. (±)-6,7-Dimethoxy-2-(3-{1-[3-(3,4-methylenedioxyphenoxy)propyl]-3-piperidyl}propanoyl)-1,2,3,4-tetrahydroisoquinoline monooxalate (34). Compound **34** was prepared from **7a** and **33** in a manner similar to that described for compound **8a** with a yield of 58%. mp: 101–105 °C (AcOEt–CH_3CN); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.47–1.50 (m, 1H), 1.67–1.89 (m, 3H), 2.03–2.07 (m, 2H), 2.67 (t, J = 5.6 Hz, 2H), 2.78 (brs, 2H), 3.10 (t, J = 7.6 Hz, 2H), 3.25–3.34 (m, 2H), 3.53 (t, J = 5.6 Hz, 2H), 3.71 (s, 6H), 3.92 (brs, 1H), 3.94 (t, J = 6.0 Hz, 2H), 4.41 (s, 2H), 5.95 (s, 2H), 6.37 (dd, J = 8.0, 2.4 Hz, 1H), 6.58 (d, J = 7.2 Hz, 1H), 6.63 (d, J = 2.4 Hz, 1H), 6.71 (s, 1H), 6.72 (s, 1H), 6.81 (d, J = 8.8 Hz, 1H); MS (FAB) m/z = 498 $(M+H)^+$. Anal. calcd for $C_{27}H_{35}N_3O_6 \cdot C_2H_2O_4 \cdot H_2O$: C, 57.51; H, 6.49; N, 6.94. Found: C, 57.28; H, 6.42; N, 6.90.

5.1.36. Methyl 6,7-dimethoxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (35). To a solution of free base of **4** (0.966 g, 5.00 mmol) and Et_3N (0.836 mL, 6.00 mmol) in THF (15.0 mL) were added dropwise methyl chloroformate (0.425 mL, 5.50 mmol) in THF (3.00 mL) at 0 °C, and the mixture was stirred at room temperature for 40 min. The mixture was concentrated in vacuo. The residue was partitioned between AcOEt and 5% (w/v) citric acid (aq), and washed with brine. The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo to give **35** (1.36 g, 100%) as colorless syrup. ^{1}H NMR (90 MHz, $CDCl_3$) δ: 2.77 (t, J = 5.8 Hz, 2H), 3.68 (t, J = 6.2 Hz, 2H), 3.79 (s, 3H), 3.85 (s, 6H), 4.55 (s, 2H), 6.59 (s, 1H), 6.62 (s, 1H); MS (FAB) m/z = 252 $(M+H)^+$.

5.1.37. 1-[3-(1,2-Benzodioxol-5-yloxy)propyl]piperidin-3-ol (37). Compound **37** was prepared from **7a** and **36** in a manner similar to that described for compound **8a** with a yield of 100%. ^{1}H NMR (90 MHz, $CDCl_3$) δ: 1.56–2.59 (m, 12H), 3.82–4.00 (m, 3H), 5.90 (s, 2H), 6.31 (dd, J = 8.5, 2.6 Hz, 1H), 6.49 (d, J = 2.4 Hz, 1H), 6.69 (d, J = 8.4 Hz, 1H); MS (EI) m/z = 279 $(M)^+$.

5.1.38. (±)-1-[3-(3,4-Methylenedioxyphenoxy)propyl]-3-piperidyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2-carboxylate monooxalate (38). To a solution of **35** (251 mg, 1.00 mmol) and **37** (419 mg, 1.50 mmol) in toluene (6.00 mL) were added NaH (60% in oil, 20 mg, 0.50 mmol), and the mixture was stirred at 140 °C for 6.5 h. After cooling at room temperature, to the mixture was added H_2O (2.00 mL), and the mixture was partitioned between $CHCl_3$ and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 99/1–98/2) to give the free base of **38** (246 mg, 0.493 mmol) as a light yellow form. To the solution of free base of **38** in MeOH (5.00 mL) was added oxalic acid (44 mg, 0.49 mmol), and the mixture was concentrated in vacuo. The crude salt was recrystallized from AcOEt–MeOH to give **38** (171 mg, 29%) as colorless powder. mp: 125–128 °C (AcOEt–MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.66 (brs, 2H), 1.83–1.86 (m, 2H), 2.03 (brs, 2H), 2.69 (t, J = 5.2 Hz, 2H), 3.01–3.03 (m, 4H), 3.22–3.35 (m, 2H), 3.56–3.63 (m, 3H), 3.71 (s, 6H), (t, J = 6.0 Hz, 2H), 4.44–4.54 (m, 2H), 4.89 (brs, 1H), 5.95 (s, 2H), 6.36 (dd, J = 8.4, 2.4 Hz, 1H), 6.62 (d, J = 2.4 Hz, 1H), 6.72–6.80 (m, 3H); MS (FAB) m/z = 499 $(M+H)^+$. Anal. calcd for $C_{27}H_{34}N_2O_7 \cdot C_2H_2O_4 \cdot 0.3H_2O$: C, 58.64; H, 6.21; N, 4.72. Found: C, 58.59; H, 6.12; N, 4.74.

5.2. Pharmacology

5.2.1. In vitro assay. Male Hartley guinea pigs (250–400 g) were sacrificed by cervical dislocation, and their hearts were removed rapidly. Right atria were cut from the heart and mounted vertically in a 30 mL organ bath containing Tyrode's solution at 37 °C and equibrated 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 (Nikon Kohden SB-1T) and measured with cardiotachometer (Nikon Kohden AT-600G) triggered by the concentration. 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.

5.3. In vivo assay

iv Study: Male Wistar rats (270–350 g) were anesthetized with urethane (1 g/kg ip). A polyethylene cannula (PE-50) was implanted in the left common carotid artery to measure blood pressure. Blood pressure was measured with a pressure transducer (Nikon Kohden DX-100) coupled to the cannula and a pressure amplifier (Nikon Kohden AP-621G), and continuously recorded via a polygraph system. Heart rate was measured with a cardiotachometer (Nikon Kohden AT-600G) triggered by the pulse wave of blood pressure. After a more than 30 min stabilization period, a test compound (or a saline) was administered intravenously through the catheter implanted into the femoral vein a dose of 3 mg/kg.

po Study: Male Wistar rats (200–300 g) were anesthetized with pentobarbital (60 mg/kg ip). A polyethylene cannula was implanted in the left common carotid artery and to measure blood pressure and heart rate, the free end of catheter was routed to an exit site at the back of the neck. The incisions were closed surgically and each rat was housed separately. The animals were allowed to recover for about 2 days after surgery, during which time they were housed in individually with free access to rat chow and water. On the day of the experiment, blood pressure was measured with a pressure transducer coupled to the cannula and a pressure amplifier, and continuously recorded via a polygraph system. Heart rate was measured with a cardiotachometer triggered by the pulse wave. After a 30 min measurement period to establish baseline values, a test compound (or a saline) was administrated orally by gavage at a dose of 10 mg/kg.

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