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Synthesis and structure–activity relationships of a series of benzazepine derivatives as 5-HT$_{2C}$ receptor agonists

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Abstract—To identify potent and selective 5-HT$_{2C}$ receptor agonists, a series of novel benzazepine derivatives were synthesized, and their structure–activity relationships examined. The compounds were evaluated for their 5-HT$_{2C}$, 5-HT$_{2A}$, and 5-HT$_{2B}$ receptor binding affinity and intrinsic activity for the 5-HT$_{2C}$ and 5-HT$_{2A}$ receptors. Among these compounds, 6,7-dichloro-2,3,4,5-tetrahydro-1*H*-3-benzazepine (**6**) was effective in a rat penile erection model when administered po, which is a symptom of the serotonin syndrome reflecting 5-HT$_{2C}$ receptor activation. Moreover, compound **6** was characterized as a partial agonist of 5-HT$_{2A}$ receptors; therefore, it had little effect on the cardiovascular system.

1. Introduction

The 5-HT$_{2C}$ receptor, one of the 14 identified subtypes of the 5-HT receptor, is of interest because of its potential as a therapy for obesity, obsessive compulsive disorder, and sexual dysfunction.[1–3] Many researchers have focused their attention on the therapeutic potential of 5-HT$_{2C}$ receptor agonists as antiobesity drugs since this has became a worldwide health issue. Indeed, the most commonly used 5-HT$_{2C}$ agonist, *m*-chlorophenylpiperazine (mCPP), is known to decrease food intake in humans[4] and rodents.[5] It is also known that mCPP's hypophagic effect in rats is attenuated by the selective-5-HT$_{2C}$ antagonist, SB-242084.[6] Moreover, some other 5-HT$_{2C}$ receptor agonists such as RO60-0175,[7] WAY-161503,[8] YM348,[9] and VER-5384[10] also have been reported to have anorectic effects in rodents.

Of these, YM348 is a novel and orally active 5-HT$_{2C}$ receptor agonist that showed high affinity (K_i = 0.89 nM) for cloned human 5-HT$_{2C}$ receptors.[11] YM348 also exerted antiobesity effects, as it not only decreased food intake, but also increased energy expenditure. One negative effect of this compound was that it increased mean arterial blood pressure (MABP) dose-dependently. However, this was completely inhibited by MDL100907,[12] a selective 5-HT$_{2A}$ antagonist. This result suggests that 5-HT$_{2A}$ receptor agonism is associated with the increases in MABP. High-throughput screening (HTS) of in-house compound libraries was conducted in the hope of discovering a novel class of 5-HT$_{2C}$ receptor agonists that had no cardiovascular effects. This led to the identification of benzazepine derivative **2** as a 5-HT$_{2C}$ receptor agonist. Compound **2** binds moderately to the 5-HT$_{2C}$ receptor (K_i = 66 nM) and was characterized as a partial 5-HT$_{2A}$ receptor agonist (E_{max} = 7%).

In this paper, the synthesis and structure–activity relationships (SAR) of a series of 3-benzazepine derivatives (**2**–**11**) are described. In addition to their binding affinities for 5-HT$_2$ receptors and efficacies for 5-HT$_{2C}$ and 5-HT$_{2A}$ receptors, a further characterization of a 5-HT$_{2C}$ receptor-mediated response, penile erection, of compound **6** is shown. In addition, compound **6** has been characterized as a partial 5-HT$_{2A}$ receptor agonist, that

Keywords: 5-HT$_{2C}$ receptor agonist; Binding affinity; Benzazepine; YM348.
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has little effect on blood pressure, which is a matter of concern with YM348 (**1**) (Fig. 1).

2. Chemistry

Synthetic routes for the substituted benzazepines **2**–**11** are shown in Schemes 1–4. Compounds **2**, **3**, **6**, and **9** were synthesized as depicted in Scheme 1. Commercially available 2-chlorophenylacetic acid (**12**) or 2,3-dichlorophenylacetic acid (**13**) was used as starting material. The condensation of each acid with 2-(methylamino)ethanol resulted in amide compounds **14** and **15**, which were reduced by BH_3 to give phenethyl amine derivatives **16** and **17**. Conversion of alcohols **16** and **17** into their corresponding chlorides with PCl_5, followed by $AlCl_3$-catalyzed cyclization, resulted in moderate yield of the seven-membered ring products **18** and **19**. Treatment of 4-chlorobenzazepine **18** with fuming nitric acid in sulfuric acid resulted in a mixture of regio-isomeric nitro derivatives. The mixture was separated by column chromatography, and the desired 5-nitro derivative **2** was isolated in the pure form in 47% yield. The methyl group on both **2** and **19** was removed using α-chloroethyl chloroformate (ACE-Cl) to afford 4-chloro-5-nitrobenzazepine (**3**) and 4,5-dichlorobenzazepine (**6**), respectively. Boc protection of benzazepine **3** followed by the reduction of the nitro group yielded 5-amino analogue **20**. Acetylation of the amino group of **20**, followed by treatment of the resultant **21** with MeI, afforded the alkylated compound **22**. Deprotection of **22** with aqueous HCl produced the 5-methylamino analogue **9**.

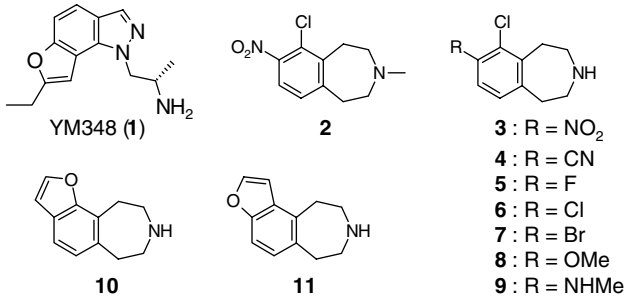
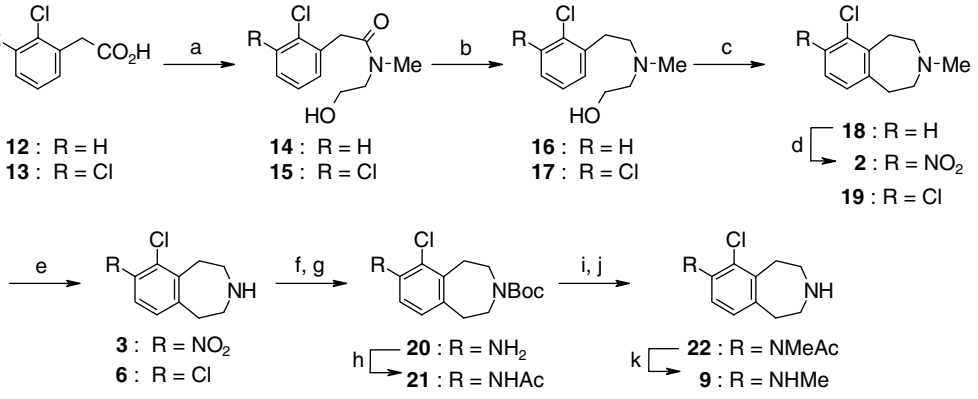


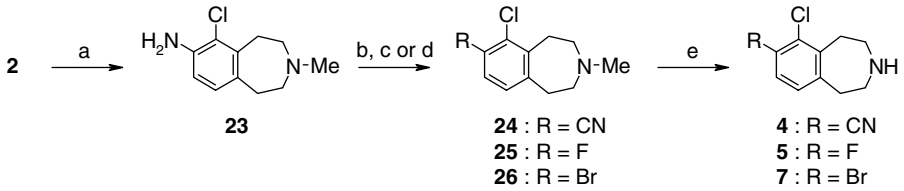
Figure 1. Structures of YM348 and benzazepines **2**–**11**.

As shown in Scheme 2, reduction of the nitro group on **2** with iron produced a good yield of the 5-amino analogue **23**. Diazotization of **23**, followed by treatment with CuCN, resulted in the 5-cyano analogue **24** in 73% yield. The diazonium salt was also treated with HF-pyridine or CuBr to yield the 5-fluoro and 5-bromo analogues **25**, **26** in 82% and 67% yield, respectively. Demethylation of the *N*-methyl compounds **24**–**26** using ACE-Cl afforded the compounds **4**, **5**, and **7**.

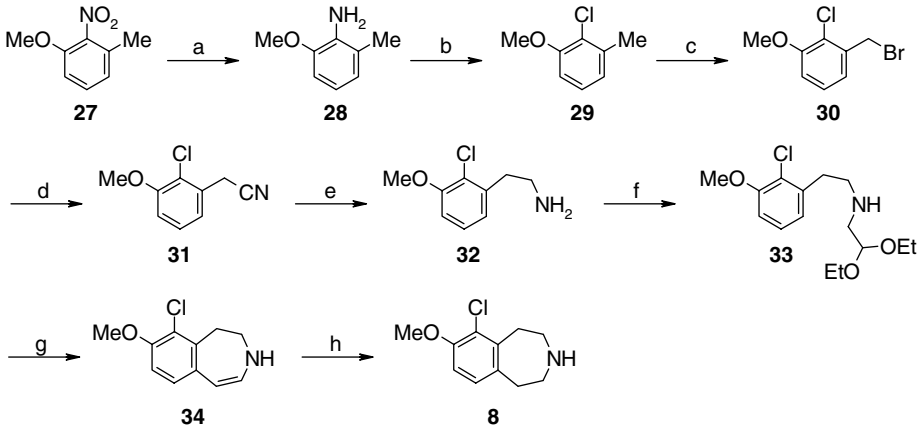
The 4-chloro-5-methoxy derivative **8** was prepared from the commercially available compound **27** using the method in Scheme 3. Thus, after hydrogenation of **27** using 10% palladium on carbon in EtOH, the corresponding aniline **28** was converted to the chloro analogue **29** with a good yield. Bromination of **29** using NBS provided **30**, to which a cyano group was then introduced, followed by reduction using $LiAlH_4$ and $AlCl_3$ to yield the phenethylamine derivative **32**. A reaction between compound **32** and bromoacetaldehyde



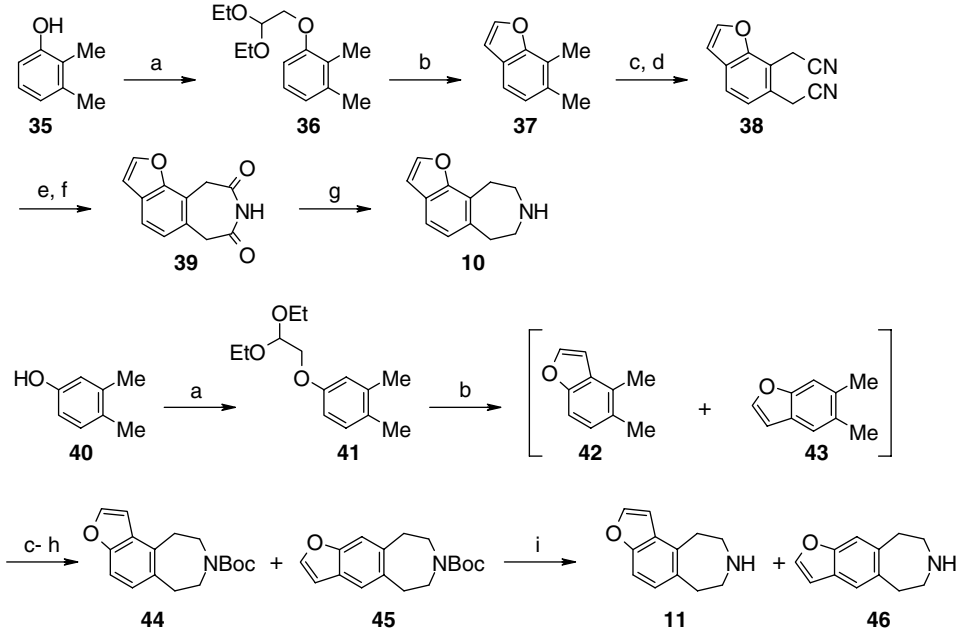
Scheme 1. Synthetic route to compounds **2**, **3**, **6**, and **9**. Reagents: (a) $SOCl_2$, then 2-(methylamino)ethanol, Et_3N, $CHCl_3$ or 2-(methylamino)ethanol, EDCI, HOBt, DMF; (b) BH_3·THF, THF; (c) PCl_5, 1,2,4-trichlorobenzene; then $AlCl_3$; (d) f-HNO_3, H_2SO_4; (e) $CH_3CH(Cl)OCOCl$; DCE, then MeOH; (f) Boc_2O, Et_3N, AcOEt; (g) Fe, NH_4Cl, EtOH, H_2O; (h) AcCl, Et_3N, THF; (i) MeI, NaH, DMF; (j) HCl, AcOEt; (k) cHCl.



Scheme 2. Synthetic route to compounds **4**, **5**, and **7**. Reagents: (a) Fe, AcOH; (b) $NaNO_2$, cHCl, then CuCN; (c) $NaNO_2$, 70% HF-pyridine; (d) $NaNO_2$, 47% HBr–H_2O; then CuBr; (e) $CH_3CH(Cl)OCOCl$, DCE, then MeOH.



Scheme 3. Synthetic route to compound **8**. Reagents: (a) Pd–C, H_2, EtOH; (b) $NaNO_2$, cHCl; acetone, H_2O, then CuCl; (c) NBS, AIBN, CCl_4; (d) KCN, *n*-$BuHSO_4$, EtOH, H_2O; (e) $LiAlH_4$, $AlCl_3$, THF; (f) $BrCH_2CH(OEt)_2$; (g) H_2SO_4; (h) $NaBH_3(CN)$, 0.5 M NaH_2PO_4aq, THF.



Scheme 4. Synthetic route to compounds **10** and **11**. Reagents and conditions: (a) $BrCH_2CH(OEt)_2$, NaH, DMF; (b) PPA, benzene; (c) NBS, AIBN, CCl_4; (d) NaCN, DMSO; (e) HBr, AcOH; (f) NaOAc, H_2O; (g) $BH_3{\cdot}Me_2S$, THF; (h) Boc_2O, THF; (i) HCl, AcOEt.

diethyl acetal afforded 2,2-diethoxyethyl derivative **33** in 45% yield, which was treated with H_2SO_4 to give the cyclized product **34** in 8% yield. Finally, reduction of **34** using sodium cyanoborohydride provided the desired compound **8**.

Scheme 4 shows the syntheses of the furan-fused compounds **10** and **11**. A reaction of 2,3-dimethylphenol (**35**) and bromoacetaldehyde diethyl acetal delivered 1-(2,2-diethoxyethoxy)-2,3-dimethylbenzene (**36**). Cyclization of the phenoxyacetal **36** using PPA provided a good yield of 6,7-dimethylbenzofuran (**37**). Bromination of **37** using NBS and AIBN in CCl_4 produced the bis(bromomethyl) compound, which was converted to the dinitrile **38** in 43% yield. Treatment of **38** with HBr in acetic acid resulted in the cyclized product **39** in 26% yield. Finally, the borane reduction of **39** produced 7,8,9,10-tetrahydro-6*H*-furo[2,3-*g*][3]benzazepine (**10**) in 56% yield. The regio-isomer **11** was obtained from 3,4-dimethylphenol (**40**) via the same reaction sequence. Cyclization of the phenoxyacetal **41** afforded an inseparable mixture of the two dimethylbenzofurans **42** and **43** with a total yield of 59% in a 1:2 ratio, respectively. The mixture of **42** and **43** was converted into an inseparable mixture of benzazepines **11** and **46** via a procedure similar to that described for **10**. The resulting compounds, **11** and **46**, were separated as their *N*-Boc derivatives **44** and **45** by silica gel column chromatography (20% and 46% yields, respectively). The Boc groups were removed from **44** and **45** to afford the benzazepine analogues **11** and **46**.

3. Results and discussion

3.1. In vitro assays

The synthesized compounds were evaluated for their 5-HT_{2C}, 5-HT_{2A}, and 5-HT_{2B} receptor binding affinity.

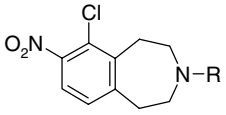
5-HT_{2C}, 5-HT_{2A}, and 5-HT_{2B} receptor binding affinities were determined using the displacement of agonist ([^{3}H]5-HT) radioligand binding to human 5-HT_{2C} and 5-HT_{2A} receptor sites in Chinese hamster ovary (CHO) cell membranes or 5-HT_{2B} receptor sites in Human Embryonic Kidney 293-Epstein–Barr virus nuclear antigen (HEK293-EBNA) cell membranes. The intrinsic activity of the compounds for the human 5-HT_{2C} and 5-HT_{2A} receptors was determined by measurement of myo-[^{3}H] inositol turnover in CHO cells. The structure–activity relationships of the novel benzazepine derivatives obtained are summarized in Tables 1–3.

As shown in Table 1, compound **2** was the first to be isolated via HTS. Although it had a lower 5-HT_{2C} affinity (K_i = 66 nM) than YM348 (**1**), compound **2** had an interesting characteristic: the intrinsic 5-HT_{2A} efficacy was very low (E_{max} = 7%). In order to improve the 5-HT_{2C} affinity, the first step taken was to eliminate the methyl group on **2**. Although the resulting NH derivative **3** showed some increase in intrinsic 5-HT_{2A} efficacy (E_{max} = 38%), the 5-HT_{2C} binding affinity improved 5-fold over that of **2** (K_i = 14 vs 66 nM). In addition, the 5-HT_{2B} receptor has been implicated in the valvular hypertrophy.[13] YM348 had only 2.8-fold selectivity over 5-HT_{2B} receptors, but compound **3** showed high selectivity over 5-HT_{2B} receptors (21-fold). For this reason, NH derivative **3** was selected as the preferred template, and optimization of the substituents on this ring was the next step.

Table 2 shows the results of substitution at the 7-position of benzazepine **3** while retaining the 6-chloro group. Replacing the 7-nitro group on compound **3** with other electron-withdrawing groups such as the cyano (**4**) and halogen (**5**–**7**) analogues resulted in some increase in 5-HT_{2C} affinities except for the fluoro derivative **5** (K_i = 5.1, 43, 8.8, and 2.4 nM, respectively). These analogues have electron-withdrawing groups that allowed them to retain their profiles as partial agonists (E_{max} = 23%, 26%, 27%, and 32%, respectively), which affects their intrinsic 5-HT_{2A} efficacy. Meanwhile the introduction of electron-donating groups, such as the methoxy (**8**) or methylamino group (**9**), to the 7-position led to some loss of 5-HT_{2C} binding affinity (K_i = 20 and 46 nM, respectively). To make matters worse, their intrinsic 5-HT_{2A} efficacy increased significantly (E_{max} = 56% and 90%) compared to those of compounds with electron-withdrawing groups (**3**–**7**) (E_{max} = 23–38%). Among the compounds evaluated, the 6,7-dichloro derivative, **6**, showed the highest selectivity over 5-HT_{2A} receptors (11-fold).

Table 3 shows the results of the furan-fused benzazepines **10** and **11**. The transformation of the dichloro benzene ring system in compound **6** to the benzofuran ring

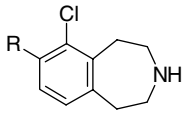
Table 1. 5-HT binding affinities and intrinsic activities of compounds **1**–**3**



Compound	R	K_i[a] (nM)			Selectivity		E_{max}[b]	
		5-HT_{2C}	5-HT_{2A}	5-HT_{2B}	2A/2C	2B/2C	5-HT_{2C}	5-HT_{2A}
YM348 (**1**)		0.89	13	2.5	15	2.8	76	97
2	Me	66	400	1000	6	15	85	7
3	H	14	51	300	4	21	86	38

[a] K_i for [^{3}H]5-HT binding; human 5-HT_{2C} or 5-HT_{2A} receptors expressed in CHO cells and 5-HT_{2B} receptors expressed in HEK293-EBNA cells.
[b] E_{max} indicates intrinsic activity and is expressed as the percentage of maximal stimulation produced by 10 μM 5-HT.

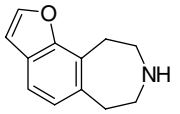
Table 2. 5-HT binding affinities and intrinsic activities of compounds **4**–**9**



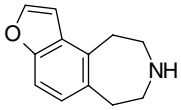
Compound	R	K_i[a] (nM)			Selectivity		E_{max}[a]	
		5-HT_{2C}	5-HT_{2A}	5-HT_{2B}	2A/2C	2B/2C	5-HT_{2C}	5-HT_{2A}
4	CN	5.1	30	65	6	13	81	23
5	F	43	130	410	3	10	80	26
6	Cl	8.8	93	100	11	11	87	27
7	Br	2.4	10	25	4	10	71	32
8	OMe	20	62	84	3	4	88	56
9	NHMe	46	90	210	2	5	81	90

[a] Refer to Table 1.

Table 3. 5-HT binding affinities and intrinsic activities of compounds **10** and **11**



10



11

Compound	K_i[a] (nM)			Selectivity		E_{max}[a]	
	5-HT_{2C}	5-HT_{2A}	5-HT_{2B}	2A/2C	2B/2C	5-HT_{2C}	5-HT_{2A}
10	23	99	34	4	1	57	40
11	20	46	90	2	5	82	47

[a] Refer to Table 1.

system was based on previous work.[14] It was anticipated that this modification would improve 5-HT_{2C} receptor affinity, but the furan-fused analogues **10** and **11** led to a loss of 5-HT_{2C} receptor binding affinity (K_i = 23 and 20 nM, respectively) and selectivity over 5-HT_{2A} receptors (2A/2C = 4- and 2-fold, respectively).

The results of SAR studies performed on benzazepine derivatives indicated that, out of those examined, compound **6** showed the most promising affinity for 5-HT_{2C} receptors and selectivity over 5-HT_{2A} and 5-HT_{2B} receptors. Therefore, compound **6** was selected for further evaluation.

3.2. In vivo activity

The 6,7-dichloro derivative **6**, which showed high 5-HT_{2C} binding affinity and the highest selectivity for 5-HT_{2A} receptors, was assessed for induction of penile erection in rats, which is a symptom of the serotonin syndrome reflecting 5-HT_{2C} receptor activation in rodents.[15] The results are presented with MED values [minimum effective dose; that is, the lowest dose that significantly ($p < 0.05$ as compared with vehicle) affected penile erections] in Table 4.

As previously reported, oral administration of YM348 (**1**) induced penile erections at a low dose (MED = 0.3 mg/kg). Compound (**6**) also showed induction of penile erections starting at a dose of 0.3 mg/kg po. As in the case of YM348 (**1**), this effect was completely inhibited by the selective 5-HT_{2C} receptor antagonist, SB242084, which indicates that 5-HT_{2C} activation was the mechanism that caused **6** to induce penile erections. Although the EC_{50} value of compound **6** for 5-HT_{2C} receptors was lower than that of YM348 (EC_{50} = 1.0 vs 38 nM), compound **6** was equipotent to YM348 in a rat penile erection model when administered po, which is a reflection of 5-HT_{2C} receptor activation in vivo.

Table 4. Functional activities for 5-HT_{2C} and 5-HT_{2A} receptors, and effect of compounds **1** and **6** on penile erections in rats after po administration

Compound	EC_{50} (nM)		MED[a] po (mg/kg)
	5-HT_{2C}	5-HT_{2A}	
YM348 (**1**)	1.0	93	0.3
6	38	260	0.3

[a] The lowest dose that significantly ($p < 0.05$ as compared with vehicle) affected penile erections was considered to be the minimum effective dose (MED).

3.3. Cardiovascular effect

Elevated blood pressure is a serious problem for obese patients. As shown in Figure 2, oral administration of YM348 (**1**) at 10 and 30 mg/kg resulted in dose-dependent increases in mean arterial blood pressure (MABP). These effects were completely inhibited by a selective 5-HT_{2A} antagonist, MDL100907. These results suggest that 5-HT_{2A} receptor agonism is associated with the increases in MABP. Therefore, the cardiovascular effect of compound **6**, which has low intrinsic 5-HT_{2A} receptor activity (E_{max} = 27%), was examined. As expected, and unlike YM348 (**1**), oral administration of compound **6** at 3, 10, and 30 mg/kg had little effect on blood pressure.

4. Conclusion

As part of the search for novel 5-HT_{2C} receptor agonists, a series of benzazepine derivatives were synthesized, and their 5-HT_{2C} agonist activity was investigated. Among these compounds, 6,7-dichloro-2,3,4,5-tetrahydro-1*H*-3-benzazepine (**6**) had good affinity and selectivity for 5-HT_{2C} receptors over 5-HT_{2A} and 5-HT_{2B} receptors. This compound was also found to be equipotent to YM348 (**1**) in a rat penile erection model when administered po, which is a reflection of 5-HT_{2C} receptor activation in vivo. Moreover, compound **6** has been characterized as a partial 5-HT_{2A} receptor agonist, that has little effect on blood pressure, which is a matter of concern with YM348 (**1**).

5. Experimental

5.1. Chemistry

Melting points were determined with a Yanaco MP-500D or a Büchi B-545 melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a

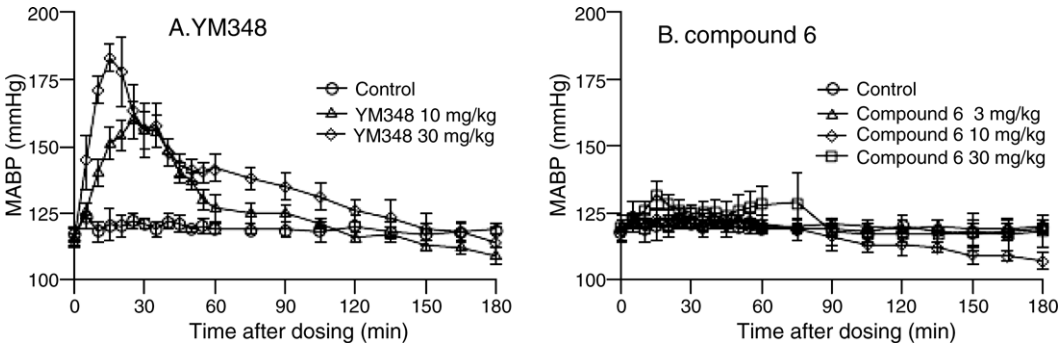


Figure 2. Effect of YM348 and compound **6** on mean arterial blood pressure (MABP) in rats. All points represent means ± SEM, $n = 5$ per group.

JEOL JNM-LA300 or a JNM-EX400 spectrometer and the chemical shifts are expressed in δ (ppm) values with tetramethylsilane as an internal standard (in NMR description: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; m, multiplet). Mass spectra were recorded on a Hitachi M-80 or a JEOL JMS-LX2000 spectrometer. Elemental analyses were performed with a Yanaco MT-5 microanalyzer (C, H, N) and a Yokogawa IC-7000S ion chromatographic analyzer (halogens), and the results were within ±0.4% of theoretical values.

5.1.1. 6-Chloro-3-methyl-7-nitro-2,3,4,5-tetrahydro-1*H*-3-benzazepine (2). To a solution of **18** (3.65 g, 18.7 mmol) in H_2SO_4 (10 mL) was added dropwise concd HNO_3 (1.30 mL, 20.6 mmol), while maintaining the temperature below 0 °C. After stirring for 1 h below 0 °C, the mixture was poured into ice-water and basified by the addition of NaOH. The aqueous phase was extracted in $CHCl_3$, and then the combined extracts were dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH/satd NH_3 aq = 50:1:0.1) to yield **2** (2.09 g, 47%) as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 2.36 (3H, s), 2.53–2.63 (4H, m), 3.00–3.07 (2H, m), 3.25–3.32 (2H, m), 7.12 (1H, d, $J = 8.0$ Hz), 7.52 (1H, d, $J = 8.0$ Hz); FAB-MS *m*/*z* 241 [(M+H)$^+$].

5.1.2. 6-Chloro-7-nitro-2,3,4,5-tetrahydro-1*H*-3-benzazepine (3). To a solution of **2** (0.36 g, 1.5 mmol) in dichloroethane (6 mL) was added α-chloroethyl chloroformate (ACE-Cl, 0.18 mL, 1.6 mmol) at room temperature, and it was heated at reflux for 5 h. The solvent was removed under reduced pressure and the residue dissolved in MeOH (6 mL). The resulting solution was heated at reflux for 2 h and evaporated. To the mixture was added H_2O (30 mL) and saturated aqueous $NaHCO_3$ (10 mL), and it was extracted with $CHCl_3$. The combined organic phases were dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 100:1–30:1) to yield **3** (0.18 g; 53%). This compound was subsequently converted to its hydrochloride. White solid, mp 235–240 °C; ^{1}H NMR(DMSO-d_6) δ 3.16–3.38 (6H, m), 3.42–3.50 (2H, m), 7.46 (1H, d, $J = 8.3$ Hz), 7.85 (1H, d, $J = 8.3$ Hz), 9.70 (2H, br s); FAB-MS *m*/*z* 227 [(M+H)$^+$]. Anal. Calcd for $C_{10}H_{11}N_2O_2Cl$·HCl: C, 45.65; H, 4.60; N, 10.65; Cl, 26.95. Found: C, 45.51; H, 4.39; N, 10.62; Cl, 26.75.

5.1.3. 6-Chloro-2,3,4,5-tetrahydro-1*H*-3-benzazepine-7-carbonitrile (4). Compound **4** was prepared from **24** using a procedure similar to that described for **3** (86%). This compound was subsequently converted to its hydrochloride. White solid, mp 233–236 °C; ^{1}H NMR (DMSO-d_6) δ 3.16–3.36 (6H, m), 3.39–3.46 (2H, m), 7.43 (1H, d, $J = 8.0$ Hz), 7.82 (1H, d, $J = 8.0$ Hz), 9.69 (2H, br s); FAB-MS *m*/*z* 207 [(M+H)$^+$]. Anal. Calcd for $C_{11}H_{11}N_2Cl$·HCl: C, 54.34; H, 4.97; N, 11.52; Cl, 29.16. Found: C, 54.28; H, 4.89; N, 11.56; Cl, 29.22.

5.1.4. 6-Chloro-7-fluoro-2,3,4,5-tetrahydro-1*H*-3-benzazepine (5). Compound **5** was prepared from **25** using a procedure similar to that described for **3** (52%). This compound was subsequently converted to its hydrochloride. White solid; ^{1}H NMR (DMSO-d_6) δ 3.08–3.28 (6H, m), 3.32–3.46 (2H, m), 7.20–7.30 (2H, m), 9.61 (2H, br s); FAB-MS *m*/*z* 200 [(M+H)$^+$]. Anal. Calcd for $C_{10}H_{11}NFCl$·HCl: C, 50.87; H, 5.12; N, 5.93; F, 8.05; Cl, 30.03. Found: C, 50.75; H, 5.01; N, 5.91; F, 8.01; Cl, 30.22.

5.1.5. 6,7-Dichloro-2,3,4,5-tetrahydro-1*H*-3-benzazepine (6). Compound **6** was prepared from **19** using a procedure similar to that described for **3** (27%). This compound was subsequently converted to its hydrochloride. White solid, mp 203–204 °C; ^{1}H NMR (DMSO-d_6) δ 3.12–3.27 (6H, m), 3.38–3.46 (2H, m), 7.24 (1H, d, $J = 8.4$ Hz), 7.48 (1H, d, $J = 8.4$ Hz), 9.51 (2H, br s); FAB-MS *m*/*z* 216 [(M+H)$^+$]. Anal. Calcd for $C_{10}H_{11}NCl_2$·HCl: C, 47.55; H, 4.79; N, 5.55; Cl, 42.11. Found: C, 47.41; H, 4.69; N, 5.56; Cl, 42.12.

5.1.6. 7-Bromo-6-chloro-2,3,4,5-tetrahydro-1*H*-3-benzazepine (7). Compound **7** was prepared from **26** using a procedure similar to that described for **3** (28%). This compound was subsequently converted to its hydrochloride. White solid, mp 263–266 °C; ^{1}H NMR (DMSO-d_6) δ 3.10–3.25 (6H, m), 3.42–3.48 (2H, m), 7.16 (1H, d, $J = 8.0$ Hz), 7.60 (1H, d, $J = 8.0$ Hz), 9.63 (2H, br s); FAB-MS *m*/*z* 260, 262 [(M+H)$^+$]. Anal. Calcd for $C_{10}H_{11}NBrCl$·HCl: C, 40.44; H, 4.07; N, 4.72; Br, 26.90; Cl, 23.87. Found: C, 40.20; H, 3.91; N, 4.69; Br, 26.92; Cl, 24.06.

5.1.7. 6-Chloro-7-methoxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine (8). To a solution of **34** (85 mg, 0.40 mmol) in THF (20 mL) were added 0.5 M aqueous NaH_2PO_4 (2 mL, 1.0 mmol) and $NaBH_3CN$ (254 mg, 4.04 mmol) at 0 °C. The reaction mixture was stirred at room temper-

ature for 1 h. To the mixture were added saturated aqueous $NaHCO_3$, and it was extracted with $CHCl_3$. The organic phases were dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 10:1) to yield **8** (53 mg, 63%) as a pale yellow oil. This compound was subsequently converted to its hydrochloride. White solid; ^{1}H NMR (DMSO-d_6) δ 3.01–3.50 (8H, m), 3.83 (3H, s), 6.97 (1H, d, J = 8.4 Hz), 7.16 (1H, d, J = 8.4 Hz), 9.13 (2H, br s); FAB-MS m/z 212 [(M+H)$^+$]. Anal. Calcd for $C_{11}H_{14}NOCl{\cdot}HCl{\cdot}0.3H_2O$: C, 52.11; H, 6.20; N, 5.52; Cl, 27.96. Found: C, 52.26; H, 5.93; N, 5.46; Cl, 27.96.

5.1.8. 6-Chloro-*N*-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-amine (9). A mixture of **22** (100 mg, 0.35 mmol) and concd HCl (2 mL) was stirred at 100 °C for 2 h. After removal of the solvent, the resulting crystals were washed with MeCN. To the crystals was added saturated aqueous $NaHCO_3$, and it was extracted with AcOEt. The combined organic phases were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH/satd NH_3 aq = 15:1:0.1) to yield **9** (34 mg, 46%). This compound was subsequently converted to its dihydrochloride. White solid, mp 242–247 °C; ^{1}H NMR (DMSO-d_6) δ 2.76 (3H, s), 3.00–3.28 (6H, m), 3.35–3.46 (2H, m), 6.58 (1H, d, J = 8.3 Hz), 7.04 (1H, d, J = 8.3 Hz), 9.57 (2H, br s); FAB-MS m/z 211 [(M+H)$^+$].

5.1.9. 7,8,9,10-Tetrahydro-6*H*-furo[2,3-*g*][3]benzazepine (10). To a solution of **39** (1.00 g, 4.65 mmol) in THF (20 mL) was added $BH_3{\cdot}Me_2S$ (1.86 mL, 10 M in Me_2S) at −20 °C, and it was stirred at room temperature for 3 h. The reaction mixture was cooled to 0 °C, then excess reagent was treated with MeOH. After stirring at this temperature for 0.5 h, concd HCl (5 mL) was added, and the mixture was stirred at room temperature for 0.5 h and basified with 1 M aqueous NaOH. The mixture was then extracted with $CHCl_3$, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH/satd NH_3 aq = 30:1:0.1–10:1:0.1) to yield **10** (488 g, 56%) as a pale yellow solid. This compound was subsequently converted to its hydrochloride. White solid; ^{1}H NMR (DMSO-d_6) δ 3.18–3.36 (6H, m), 3.36–3.50 (2H, m), 6.94 (1H, d, J = 2.0 Hz), 7.12 (1H, d, J = 7.8 Hz), 7.44 (1H, d, J = 7.8 Hz), 7.98 (1H, d, J = 2.0 Hz), 9.32 (2H, br s); FAB-MS m/z 188 [(M+H)$^+$].

5.1.10. 7,8,9,10-Tetrahydro-6*H*-furo[3,2-*g*][3]benzazepine (11). To a solution of **44** (110 mg, 0.38 mmol) in AcOEt (5 mL) was added HCl–AcOEt (4 M, 10 mL) at 0 °C, and it was stirred at room temperature for 3 h. After cooling to 0 °C, to the reaction mixture was added diisopropylether (10 mL), and the resulting precipitate was collected by filtration to yield **11** (74 mg, 87%) as its hydrochloride. White solid, mp 227–229 °C; ^{1}H NMR (DMSO-d_6) δ 3.12–3.26 (6H, m), 3.27–3.42 (2H, m), 7.08 (1H, d, J = 2.0 Hz), 7.16 (1H, d, J = 8.4 Hz), 7.39 (1H, d, J = 8.4 Hz), 7.97 (1H, d, J = 2.0 Hz), 9.52 (2H, br s); FAB-MS m/z 188 [(M+H)$^+$]. Anal. Calcd for $C_{12}H_{13}NO{\cdot}HCl$: C, 64.43; H, 6.31; N, 6.26; Cl, 15.85. Found: C, 64.39; H, 6.29; N, 6.25; Cl, 16.11.

5.1.11. 2-(2-Chlorophenyl)-*N*-(2-hydroxyethyl)-*N*-methylacetamide (14). To a solution of (2-chlorophenyl)acetic acid **12** (25.0 g, 146 mmol) in DMF (250 mL) were added HOBt (23.7 g, 176 mmol), 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (33.7 g, 176 mmol), and 2-(methylamino)ethanol (13.2 g, 176 mmol) at room temperature, and it was stirred at room temperature for 2 h. The reaction mixture was diluted with AcOEt, washed with 1 M aqueous HCl, H_2O, 1 M aqueous NaOH, and brine, after which it was dried over $MgSO_4$ and concentrated in vacuo to yield **14** (16.4 g, 49%) as a white solid. ^{1}H NMR (DMSO-d_6) δ 2.85 (1.68H, s), 3.09 (1.32H, s), 3.33–3.39 (1H, m), 3.42–3.50 (2H, m), 3.56–3.63 (1H, m), 3.77 (0.88H, s), 3.85 (1.12H, s), 4.65 (0.44H, t, J = 5.3 Hz), 4.89 (0.56H, t, J = 5.3 Hz), 7.23–7.31 (3H, m), 7.37–7.44 (1H, m); FAB-MS m/z 228 [(M+H)$^+$].

5.1.12. 2-(2,3-Dichlorophenyl)-*N*-(2-hydroxyethyl)-*N*-methylacetamide (15). Compound **15** was prepared from (2,3-dichlorophenyl)acetic acid **13** using a procedure similar to that described for **14** as a white solid (52%). ^{1}H NMR (DMSO-d_6) δ 2.85 (1.68H, s), 3.11 (1.32H, s), 3.32–3.39 (1H, m), 3.43–3.53 (2H, m), 3.56–3.64 (1H, m), 3.86 (0.88H, s), 3.94 (1.12H, s), 4.66 (0.44H, t, J = 5.3 Hz), 4.91 (0.56H, t, J = 5.3 Hz), 7.22–7.35 (3H, m), 7.48–7.56 (1H, m); FAB-MS m/z 262 [(M+H)$^+$].

5.1.13. 2-[[2-(2-Chlorophenyl)ethyl](methyl)amino]ethanol (16). To a solution of **14** (18.2 g, 80.0 mmol) in THF (100 mL) was added $BH_3{\cdot}$THF (240 mL, 1 M in THF) at 0 °C, and it was stirred at room temperature for 0.5 h. To the reaction mixture was added MeOH (20 mL) at 0 °C. After stirring at this temperature for 0.5 h, 6 M aqueous HCl (100 mL) was added, and the mixture was stirred at room temperature for 0.5 h and then concentrated in vacuo. After addition of H_2O (100 mL) and NaOH (40 g) while cooling in an ice bath, the mixture was extracted with $CHCl_3$, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH/satd NH_3 aq = 50:1:0.1) to yield **16** (14.2 g, 83%) as pale yellow oil. ^{1}H NMR (DMSO-d_6) δ 2.26 (3H, s), 2.44–2.60 (4H, m), 2.79–2.87 (2H, m), 3.44–3.50 (2H, m), 4.32 (1H, t, J = 5.5 Hz), 7.17–7.30 (2H, m), 7.23–7.44 (2H, m); FAB-MS m/z 214 [(M+H)$^+$].

5.1.14. 2-[[2-(2,3-Dichlorophenyl)ethyl](methyl)amino]ethanol (17). Compound **17** was prepared from **15** using a procedure similar to that described for **16** as a white solid (81%). ^{1}H NMR (DMSO-d_6) δ 2.26 (3H, s), 2.43–2.52 (2H, m), 2.54–2.62 (2H, m), 2.85–2.93 (2H, m), 3.41–3.44 (2H, m), 4.32 (1H, t, J = 5.5 Hz), 7.25–7.32 (1H, m), 7.36 (1H, dd, J = 1.7, 7.7 Hz), 7.48 (1H, dd, J = 1.7, 7.7 Hz); FAB-MS m/z 248 [(M+H)$^+$].

5.1.15. 6-Chloro-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (18). To a solution of **16** (14.0 g, 65.5 mmol) in 1,2,4-trichlorobenzene (85 mL) was added PCl_5 (5.21 g, 25.0 mmol), and it was stirred at 110 °C for 0.5 h. To

the reaction mixture was added portionwise $AlCl_3$ (17.5 g, 131 mmol), and it was stirred at 200 °C for 5 h. After cooling to 50 °C, to the mixture were added H_2O (300 mL) and concd HCl (13 mL). After stirring at room temperature for 0.5 h, the mixture was extracted with H_2O. The aqueous layer was basified with 50% aqueous NaOH and extracted with toluene. The combined organic phases were washed with H_2O and evaporated. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH/satd NH_3 aq = 50:1:0.1) to yield **18** (5.74 g, 45%) as brown oil. ^{1}H NMR (DMSO-d_6) δ 2.23 (3H, s), 2.42–2.52 (4H, m), 2.87–2.95 (2H, m), 3.12–3.19 (2H, m), 7.14 (1H, d, J = 8.1 Hz), 7.37 (1H, d, J = 8.1 Hz); EI-MS m/z 195 [M^+].

5.1.16. 6,7-Dichloro-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (19). Compound **19** was prepared from **17** using a procedure similar to that described for **18** to yield a yellow oil (37%). ^{1}H NMR ($CDCl_3$) δ 2.37 (3H, s), 2.50–2.65 (4H, m), 2.90–3.00 (2H, m), 3.15–3.25 (2H, m), 6.96–7.06 (2H, m), 7.19–7.27 (1H, m); EI-MS m/z 229 [M^+].

5.1.17. *tert*-Butyl 7-amino-6-chloro-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carboxylate (20). To a solution of a hydrochloride salt of **3** (0.95 g, 3.6 mmol) in AcOEt (15 mL) were added Boc_2O (0.82 g, 3.8 mmol) and Et_3N (0.53 mL, 3.8 mmol) at 0 °C, and it was stirred at room temperature for 5 h. To the mixture was added H_2O (50 mL), and it was extracted with AcOEt. The combined organic phases were washed with 5% aqueous $NaHSO_4$, H_2O, and brine, and dried over Na_2SO_4. After removal of the solvent, the residue was washed with hexane to yield the *N*-Boc derivative (1.07 g, 91%) as a pale yellow solid which was used directly for the next step without further purification.

The *N*-Boc derivative was dissolved with EtOH (8 mL), and then added H_2O (3 mL), Fe (0.78 g, 14 mmol), and NH_4Cl (75 mg, 1.4 mmol). After stirring at room temperature for 15 h, the reaction mixture was filtered through Celite and the solvent was removed in vacuo. The resulting residue was purified by column chromatography on silica gel (AcOEt/hexane = 1:10–1:7) to yield **20** (0.30 g, 36%) as a pale yellow solid. ^{1}H NMR ($CDCl_3$) δ 1.46 (9H, s), 2.77–2.86 (2H, m), 3.08–3.16 (2H, m), 3.47–3.60 (4H, m), 6.56 (1H, d, J = 8.1 Hz), 6.82 (1H, d, J = 8.1 Hz); FAB-MS m/z 296 [M^+].

5.1.18. *tert*-Butyl 7-(acetylamino)-6-chloro-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carboxylate (21). To a solution of **20** (0.35 g, 1.18 mmol) in THF (4 mL) were added Et_3N (0.17 mL, 1.22 mmol) and AcCl (90 μL, 1.27 mmol) at 0 °C, and it was stirred at room temperature for 5 h. To the mixture was added H_2O, and it was then extracted with AcOEt. The combined organic phases were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (AcOEt/hexane = 1:5–1:3) to yield **21** (0.33 g, 83%) as white amorphous solid. ^{1}H NMR ($CDCl_3$) δ 1.46 (9H, s), 2.85–2.95 (2H, m), 3.11–3.19 (2H, m), 3.49–3.61 (4H, m), 7.03 (1H, d, J = 8.2 Hz), 8.10 (1H, d, J = 8.2 Hz); FAB-MS m/z 339 [$(M+H)^+$].

5.1.19. *N*-(6-Chloro-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-*N*-methylacetamide (22). To a solution of **21** (0.23 g, 0.68 mmol) in DMF (3 mL) were added 60% NaH (30 mg, 0.75 mmol) and MeI (50 μL, 0.80 mmol) at 0 °C, and it was stirred at room temperature for 5 h. To the mixture was added H_2O, and it was extracted with AcOEt. The combined organic phases were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (AcOEt/hexane = 1:3–1:1) to yield *N*-methyl derivative (0.21 g) as a white amorphous solid that was used directly for the next step without further purification.

The *N*-methyl derivative was dissolved with $CHCl_3$ (5 mL), and then added 4 M HCl–AcOEt (1.5 mL). After stirring at room temperature for 5 h, the solvent was removed. The resulting crystal was washed with AcOEt to yield **22** (0.16 g, 93%) as the hydrochloride salt. White solid; ^{1}H NMR (DMSO-d_6) δ 1.67 (3H, s), 3.04 (3H, s), 3.05–3.35 (6H, m), 3.40–3.50 (2H, m), 7.31 (1H, d, J = 8.1 Hz), 7.36 (1H, d, J = 8.1 Hz), 9.58 (2H, br s); FAB-MS m/z 253 [$(M+H)^+$].

5.1.20. 6-Chloro-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-amine (23). Compound **2** (2.09 g, 8.63 mmol) was dissolved with AcOH (20 mL), and then Fe (2.42 g, 43.2 mmol) was added. After stirring at 70 °C for 2 h, the reaction mixture was filtered through Celite and the solvent was removed in vacuo. The resulting residue was diluted with $CHCl_3$, washed with saturated aqueous $NaHCO_3$, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH/satd NH_3 aq = 20:1:0.1) to yield **23** (1.62 g, 89%) as a pale brown solid. ^{1}H NMR (DMSO-d_6) δ 2.21 (3H, s), 2.35–2.44 (4H, m), 2.69–2.76 (2H, m), 2.97–3.05 (2H, m), 5.02 (2H, s), 6.53 (1H, d, J = 8.1 Hz), 6.77 (1H, d, J = 8.1 Hz); EI-MS m/z 240 [M^+].

5.1.21. 6-Chloro-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine-7-carbonitrile (24). H_2O (30 mL) and then concd H_2SO_4 (1.52 mL, 28.5 mmol) were added to compound **23** (3.00 g, 14.2 mmol). A solution of $NaNO_2$ (1.18 g, 17.1 mmol) in H_2O (10 mL) was added to the mixture at 0–5 °C. After stirring at 0 °C for 0.5 h, to the mixture were added toluene (20 mL), $NaHCO_3$ (4.8 g, 57.1 mmol), and H_2O (10 mL). The reaction mixture was added to a solution of CuCN (3.19 g, 35.6 mmol), KCN (6.32 g, 97 mmol), H_2O (40 mL), and AcOEt (50 mL). After stirring at 70 °C for 2 h, the reaction mixture was diluted with AcOEt, washed with brine, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH/satd NH_3 aq = 20:1:0.1) to yield **24** (2.30 g, 73%) as a pale green solid. ^{1}H NMR (DMSO-d_6) δ 2.24 (3H, s), 2.41–2.49 (4H, m), 2.87–3.02 (2H, m), 3.10–3.20 (2H, m), 7.34 (1H, d, J = 8.0 Hz), 7.30 (1H, d, J = 8.0 Hz); FAB-MS m/z 221 [$(M+H)^+$].

5.1.22. 6-Chloro-7-fluoro-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (25). Compound **23** (0.58 g, 2.75 mmol) was added to 48% aqueous HBF_4 (1.26 mL, 9.63 mmol) at 0 °C. To the mixture was added portionwise $NaNO_2$

(0.19 g, 2.75 mmol), and it was stirred at 0 °C for 1 h. After removal of the solvent, the mixture was stirred at 160 °C for 3 h. After cooling, to the reaction mixture was added saturated aqueous NH_3, which was then extracted with $CHCl_3$, dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH/satd NH_3 aq = 97:3:0.3) to yield **25** (0.48 g, 82%) as a pale brown oil. ^{1}H NMR (DMSO-d_6) δ 2.24 (3H, s), 2.40–2.50 (4H, m), 2.86–2.94 (2H, m), 3.06–3.13 (2H, m), 7.11–7.17 (2H, m); EI-MS *m/z* 213 [M^+].

5.1.23. 7-Bromo-6-chloro-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (26). A mixture of **23** (0.80 g, 3.80 mmol) and 47% aqueous HBr (3.3 mL) was refluxed for 0.5 h. After cooling to 0 °C, to the mixture was added portionwise $NaNO_2$ (0.26 g, 3.80 mmol) at 0–10 °C. After stirring for 0.5 h at 0 °C, the reaction mixture was added dropwise to a solution of CuBr (0.65 g, 4.56 mmol) and 47% aqueous HBr (1.3 mL) at 0 °C. After stirring at 0 °C for 2 h, the reaction mixture was poured into ice-water and basified with saturated aqueous NH_3. The solution was extracted with $CHCl_3$ and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH/satd NH_3 aq = 97:3:0.3) to yield **26** (0.70 g, 67%) as a colorless oil. ^{1}H NMR (DMSO-d_6) δ 2.23 (3H, s), 2.41–2.49 (4H, m), 2.86–2.93 (2H, m), 3.14–3.21 (2H, m), 7.07 (1H, d, J = 7.9 Hz), 7.51 (1H, d, J = 7.9 Hz); FAB-MS *m/z* 274, 276 [$(M+H)^+$].

5.1.24. 2-Methoxy-6-methylaniline (28). To a solution of 1-methoxy-3-methyl-2-nitrobenzene **27** (10.0 g, 59.8 mmol) in EtOH (300 mL) was added 10% Pd on carbon (1.88 g). The mixture was stirred at room temperature for 2 h under H_2. The catalyst was removed by filtration through Celite and the solvent was removed in vacuo. The resulting residue was purified by column chromatography on silica gel (AcOEt/hexane = 1:9) to yield **28** (8.20 g, quant.) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 2.18 (3H, s), 3.85 (3H, s), 3.74 (2H, br s), 6.64–6.74 (3H, m).

5.1.25. 2-Chloro-1-methoxy-3-methylbenzene (29). To a solution of **28** (8.20 g, 59.8 mmol) in acetone (160 mL) and H_2O (25 mL) was added concd HCl (20 mL). A solution of $NaNO_2$ (4.54 g, 65.8 mmol) in H_2O (13 mL) was added dropwise to the mixture at 0–5 °C. After stirring for 0.5 h at 0 °C, to the mixture was added CuCl (6.51 g, 65.8 mmol). After stirring at room temperature for 1 h, the reaction mixture was diluted with AcOEt, washed with H_2O and brine, and then dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (AcOEt/hexane = 1:10) to yield **29** (8.15 g, 87%) as a colorless oil. ^{1}H NMR (DMSO-d_6) δ 2.32 (3H, s), 3.83 (3H, s), 6.93 (1H, d, J = 7.9 Hz), 6.97 (1H, d, J = 7.9 Hz), 7.19 (1H, t, J = 7.9 Hz).

5.1.26. 1-(Bromomethyl)-2-chloro-3-methoxybenzene (30). To a solution of **29** (4.00 g, 25.5 mmol) in CCl_4 (50 mL) were added NBS (4.32 g, 24.3 mmol) and AIBN (40 mg). The reaction mixture was heated at reflux for 2 h. After cooling, to the mixture was added saturated aqueous $NaHCO_3$, and it was extracted with $CHCl_3$ and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (AcOEt/hexane = 1:10) to yield **30** (5.94 g, quant.) as a colorless oil. ^{1}H NMR (DMSO-d_6) δ 3.86 (3H, s), 4.73 (2H, s), 7.14 (1H, dd, J = 1.5, 8.3 Hz), 7.18 (1H, dd, J = 1.5, 8.3 Hz), 7.31 (1H, t, J = 8.3 Hz).

5.1.27. 2-(2-Chloro-3-methoxyphenyl)ethanamine (32). To a solution of **30** (5.90 g, 25.1 mmol) in EtOH (30 mL) and H_2O (30 mL) were added KCN (1.79 g, 27.5 mmol) and n-Bu_4HSO_4 (40 mg) at 0 °C. The reaction mixture was stirred at 50 °C for 4 h. After cooling, the mixture was poured into water and extracted with AcOEt. The organic extracts were washed with H_2O and brine, and then dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (AcOEt/hexane = 1:3) to yield (2-chloro-3-methoxyphenyl)acetonitrile **31** (3.12 g, 68%) as a white solid.

To a stirred suspension of $LiAlH_4$ (0.75 mg, 19 mmol) in THF (50 mL) was added portionwise $AlCl_3$ at −20 °C. After stirring at 0 °C for 0.5 h, to the mixture was added a solution of **31** (3.00 g, 16.5 mmol) in THF (10 mL) dropwise at 0 °C, and it was stirred at room temperature for 3 h. The excess reagent was quenched by the addition of MeOH, followed by the addition of 15% aqueous NaOH (0.75 mL) and water (2.5 mL). After stirring for 0.5 h, the mixture was filtered with Celite and concentrated in vacuo to yield the crude product, which was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 10:1) to yield **32** (2.19 g; 71%). ^{1}H NMR ($CDCl_3$) δ 3.00–3.14 (4H, m), 3.89 (3H, s), 4.26 (2H, br s), 6.83 (1H, dd, J = 1.3, 8.0 Hz), 6.90 (1H, dd, J = 1.3, 8.0 Hz), 7.17 (1H, t, J = 8.0 Hz).

5.1.28. *N*-[2-(2-Chloro-3-methoxyphenyl)ethyl]-2,2-diethoxyethanamine (33). To a solution of **32** (2.10 g, 11.3 mmol) in DMF (40 mL) were added K_2CO_3 (7.80 g, 56.4 mmol) and bromoacetaldehyde diethyl acetal (2.29 g, 11.6 mmol). The reaction mixture was stirred at 50 °C for 6 h. After cooling to room temperature, the mixture was poured into cold water and extracted with AcOEt. The organic extracts were washed with H_2O, brine and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 100:1) to yield **33** (1.53 g, 45%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.20 (6H, t, J = 7.0 Hz), 2.77 (2H, d, J = 5.6 Hz), 2.86–2.98 (4H, m), 3.50–3.58 (2H, m), 3.64–3.74 (2H, m), 3.89 (3H, s), 4.60 (1H, t, J = 5.6 Hz), 6.81 (1H, dd, J = 1.3, 8.2 Hz), 6.87 (1H, dd, J = 1.3, 8.2 Hz), 7.15 (1H, t, J = 8.2 Hz).

5.1.29. 9-Chloro-8-methoxy-2,3-dihydro-1*H*-3-benzazepine (34). Compound **33** (1.50 g, 4.97 mmol) was added to concd H_2SO_4 (10 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. After cooling, the mixture was poured into cold water and basified with 2 M aqueous NaOH. The aqueous phase was extracted with AcOEt. The combined organic phases were washed with H_2O and brine, and then dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel

($CHCl_3$/MeOH = 100:1–10:1) to yield **34** (85 mg, 8%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 3.27–3.35 (2H, m), 3.41–3.50 (2H, m), 3.86 (3H, s), 3.98 (1H, br s), 5.04 (1H, d, J = 9.9 Hz), 6.10–6.18 (1H, m), 6.72 (1H, d, J = 8.4 Hz), 6.93 (1H, d, d = 8.4 Hz).

5.1.30. 1-(2,2-Diethoxyethoxy)-2,3-dimethylbenzene (36). To a suspension of 60% NaH (4.72 g, 118 mmol) in DMF (100 mL) was slowly added 2,3-dimethylphenol **35** (10.0 g, 81.9 mmol) at 0 °C. After stirring at this temperature for 0.5 h, to the reaction mixture was added bromoacetaldehyde diethylacetal (19.37 g, 98.3 mmol), and it was then heated at 170 °C for 3 h. After cooling to room temperature, the reaction mixture was poured into ice-water and extracted with AcOEt. The combined extracts were washed with 1 M aqueous NaOH, H_2O, and brine, and then dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (AcOEt/hexane = 1:9) to yield **36** (15.8 g, 81%) as a colorless oil. ^{1}H NMR (DMSO-d_6) δ 1.15 (3H, t, J = 7.1 Hz), 2.08 (3H, s), 2.20 (3H, s), 3.52–3.75 (4H, m), 3.90 (1H, d, J = 5.3 Hz), 4.81 (1H, t, J = 5.3 Hz), 6.76 (1H, d, J = 7.9 Hz), 6.78 (1H, d, J = 7.9 Hz), 7.01 (1H, t, J = 7.9 Hz).

5.1.31. 6,7-Dimethyl-1-benzofuran (37). To a solution of **36** (15.0 g, 62.9 mmol) in benzene (200 mL) was added PPA (15.0 g) at room temperature, and the reaction mixture was heated at reflux for 2 h. After cooling to room temperature, the benzene layer was decanted from the PPA, diluted with ether, washed with saturated aqueous $NaHCO_3$, H_2O, and brine, and then dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (AcOEt/hexane = 1:100) to yield **37** (7.34 g, 80%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 2.38 (3H, s), 2.44 (3H, s), 6.70 (1H, d, J = 2.2 Hz), 7.04 (1H, d, J = 7.7 Hz), 7.30 (1H, d, J = 7.7 Hz), 7.56 (1H, d, J = 2.2 Hz).

5.1.32. 2,2′-(1-Benzofuran-6,7-diyl)diacetonitrile (38). To a solution of **37** (7.20 g, 49.3 mmol) in CCl_4 (100 mL) were added NBS (17.5 g, 98.5 mmol) and AIBN (100 mg). The reaction mixture was heated at reflux for 3 h. After cooling to room temperature, the reaction mixture was filtered through Celite, and the filtrate was evaporated in vacuo. The residue was diluted with ether, washed with saturated aqueous $NaHCO_3$, H_2O, and brine, dried over $MgSO_4$, and evaporated in vacuo to afford crude 6,7-bis(bromomethyl)-1-benzofuran as a yellow solid with was used directly for the next step without further purification.

To the obtained yellow solid, DMSO (70 mL) and NaCN (7.25 g, 150 mmol) were added, and the reaction mixture was stirred at room temperature for 3 h. The mixture was poured into ice-water and extracted with AcOEt. The combined extracts were washed with H_2O and brine, and then dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (AcOEt/hexane = 1:3) to yield **38** (4.17 g, 43%) as a yellow solid. ^{1}H NMR (DMSO-d_6) δ 4.23 (3H, s), 4.31 (3H, s), 7.05 (1H, d, J = 2.4 Hz), 7.37 (1H, d, J = 8.0 Hz), 7.71 (1H, d, J = 8.0 Hz), 8.14 (1H, d, J = 2.4 Hz); FAB-MS m/z 196 [$(M+H)^+$].

5.1.33. 6*H*-Furo[2,3-*g*][3]benzazepine-7,9(8*H*,10*H*)-dione (39). Compound **38** (3.50 g, 17.8 mmol) was dissolved in AcOH (15 mL), and then HBr (33% in AcOH, 30 g) was added. After stirring at room temperature for 5 h, the reaction mixture was poured into ice-water, and the resulting precipitate was collected by filtration and dried in vacuo to yield a yellow solid (2.54 g) that was used directly for the next step without further purification.

H_2O (50 mL) and NaOAc (2.22 g, 27.1 mmol) were added to the yellow solid, and the reaction mixture was heated at reflux for 1 h. After cooling to room temperature, the resulting precipitate was collected by filtration and dried in vacuo. The resulting crude product was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 30:1) to yield **39** (1.01 g, 26%) as a yellow solid. ^{1}H NMR (DMSO-d_6) δ 4.20 (3H, s), 4.35 (3H, s), 6.99 (1H, d, J = 2.2 Hz), 7.24 (1H, d, J = 7.9 Hz), 7.55 (1H, d, J = 7.9 Hz), 8.03 (1H, d, J = 2.2 Hz), 10.49 (1H, br s).

5.1.34. 4-(2,2-Diethoxyethoxy)-1,2-dimethylbenzene (41). Compound **41** was prepared from 3,4-dimethylphenol **40** using a procedure similar to that described for **36** (73%). ^{1}H NMR ($CDCl_3$) δ 1.24 (3H, t, J = 7.0 Hz), 2.18 (3H, s), 2.22 (3H, s), 3.57–3.82 (4H, m), 3.97 (1H, d, J = 5.2 Hz), 4.82 (1H, t, J = 5.2 Hz), 6.66 (1H, dd, J = 2.6, 8.0 Hz), 6.74 (1H, d, J = 2.6 Hz), 7.01 (1H, d, J = 8.0 Hz); FAB-MS m/z 238 [M^+].

5.1.35. *tert*-Butyl 6,7,9,10-tetrahydro-8*H*-furo[3,2-*g*]-[3]benzazepine-8-carboxylate (44) and *tert*-butyl 5,6,8,9-tetrahydro-7*H*-furo[2,3-*h*][3]benzazepine-7-carboxylate (45). A mixture of **11** and **46** was prepared from **41** using a procedure similar to that described for **37**, **38**, **39**, and **10**, in 59%, 21%, 61%, and 50% yield. The mixture of **11** and **46** (**11**/**46** = 1:2, 400 mg, 2.14 mmol) was dissolved with THF (20 mL), and added Boc_2O (930 mg, 4.28 mmol). After stirring at room temperature for 1 h, the solvent was evaporated and the resulting residue was purified by column chromatography on silica gel (AcOEt/hexane = 20:1) to yield **44** (120 mg, 20%) as a colorless oil and **45** (284 mg, 46%) as a colorless oil.

Compound **44**: ^{1}H NMR ($CDCl_3$) δ 1.48 (9H, s), 2.94–3.03 (2H, m), 3.07–3.14 (2H, m), 3.53–3.68 (4H, m), 6.76 (1H, d, J = 2.1 Hz), 7.06 (1H, d, J = 8.3 Hz), 7.26 (1H, d, J = 8.3 Hz), 7.59 (1H, d, J = 2.1 Hz); FAB-MS m/z 288 [$(M+H)^+$].

Compound **45**: ^{1}H NMR ($CDCl_3$) δ 1.48 (9H, s), 2.92–3.03 (4H, m), 3.52–3.63 (4H, m), 6.68 (1H, dd, J = 0.8, 2.1 Hz), 7.27 (1H, s), 7.33 (1H, s), 7.56 (1H, d, J = 2.1 Hz); FAB-MS m/z 288 [$(M+H)^+$].

5.1.36. 6,7,8,9-Tetrahydro-5*H*-furo[2,3-*h*][3]benzazepine (46). The hydrochloride salt of **46** was prepared from **45** using a procedure similar to that described for **11** (52%). White solid; ^{1}H NMR (DMSO-d_6) δ 3.10–3.28 (8H, m), 6.89 (1H, d, J = 2.0 Hz), 7.47 (1H, s), 7.48

(1H, s), 7.95 (1H, d, $J = 2.0$ Hz), 9.54 (2H, br s); FAB-MS *m/z* 188 [$(M+H)^+$]. Anal. Calcd for $C_{12}H_{13}NO{\cdot}HCl$: C, 64.43; H, 6.31; N, 6.26; Cl, 15.85. Found: C, 64.17; H, 6.43; N, 6.19; Cl, 16.07.

5.2. Biological procedures

5.2.1. Receptor binding assay. The membrane preparation was washed once with 50 mM Tris–HCl buffer (pH 7.4) containing 4 mM $CaCl_2$ just before it was used for the binding assays. The 5-HT_{2C}, 5-HT_{2A}, and 5-HT_{2B} receptor binding assays with [^{3}H]5-HT were carried out using the methods of Pazos et al.[16] with a slight modification; reaction medium [50 mM Tris–HCl buffer (pH 7.4) containing 4 mM $CaCl_2$, 10 μM pargyline, and 0.1 mg/mL *l*-(+)-ascorbic acid] containing [^{3}H]5-HT, membrane preparation, and test compounds was incubated at 37 °C for 30 min. Non-specific binding was determined in the presence of 10 μM 5-HT, and specific binding was calculated as total binding minus non-specific binding. After incubation, 4 mL of 50 mM Tris–HCl buffer (pH 7.4) containing 4 mM $CaCl_2$ was added, and the medium was filtered under vacuum through Whatman GF/B glass filter pre-treated with 0.1% polyethyleneimine. The filter was washed with the same buffer solution (3× 4 mL). The GF/B glass filter was immersed in 6 mL of liquid scintillator (Packard, Aquasol-2), and radioactivities were measured with a liquid scintillation counter (Packard, Tri-Carb-2500TR). The amounts of protein were measured according to the method established by Lowry et al.[17] Dissociation constants (K_d value) were obtained by Scatchard analysis using SAS (ver. 6.11) together with an application software developed by our company (5-HT_{2C}; 1.6 nM, 5-HT_{2A}; 9.8 nM, and 5-HT_{2B}; 14 nM). Concentrations of compounds showing 50% inhibition of receptor binding, IC_{50} values, were obtained by non-linear analysis using SAS (ver. 6.11) together with an application software developed by our company. K_i values indicating affinity for receptors were calculated by using a formula developed by Cheng and Prussoff.[18]

5.2.2. PI hydrolysis assay. PI hydrolysis assay was carried out using the methods of Aramori et al.[19] with a slight modification. Human 5-HT_{2C} and 5-HT_{2A} receptor expressing CHO cells were seeded onto a 24-well plate (approximately 1×105 cells/well), and cultured for 1 day. After the addition of myo-[^{3}H]inositol (3 μCi/mL), they were incubated for 24 h for labeling. After the cells were washed two times with phosphate-buffered saline (PBS), they were incubated with PBS for 20 min and then further incubated with PBS–LiCl solution for 20 min. After 20-min incubation with PBS–LiCl solution containing the test compound, the reaction was terminated by adding 0.2 M PCA, after which the reaction mixture was allowed to stand at 4 °C for 1–3 h. After 2 M KOH and 100 mM EDTA–2Na solution were added, the plate was centrifuged (2000 rpm, 5 min). The supernatant (1 mL) was added to a Bio-Rad AG1-X8 column and washed with GPI solution (5 mM disodium tetraborate, 60 mM sodium formate) (2× 3.5 mL), and eluted with 4 mL of IP3 solution (0.1 M formate, 1 M ammonium formate). The elute was added to a liquid scintillator (Aquasol-2) and measured with the liquid scintillation counter. EC_{50} values and E_{max} (%) were calculated by non-linear analysis using SAS (ver. 6.11) together with an application software developed by our company. E_{max} (%) indicated intrinsic activity and the response produced by 10 μM 5-HT was defined as 100%.

5.2.3. Behavioral studies. All experiments were carried out during 13:00–19:00. Rats were placed individually in transparent acrylic plastic cages to count the number of penile erections. A penile erection was defined as previously described[20]: repeated pelvic thrusts immediately followed by assuming an upright position (on hind limbs), an emerging, engorged penis, and licking it. The number of penile erections was observed for 30 min immediately after test compounds' po administration.

5.2.4. Cardiovascular effect. The rats were anesthetized with pentobarbital sodium (60 mg/kg ip), and a catheter was inserted into the carotid artery to measure the systemic arterial pressure. The rats were used in the study after a postoperative recovery period of two or more days. After conscious animals were housed in cages for blood pressure measurement and stabilized for at least 30 min, YM348 (10–30 mg/kg) or compound **6** (3–30 mg/kg) was administered orally.

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