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7-Chloro-5-hydroxy-1-[2-methyl-4-(2-methylbenzoyl-amino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine (OPC-41061): A Potent, Orally Active Nonpeptide Arginine Vasopressin V_2 Receptor Antagonist

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Abstract—We previously reported a series of benzazepine derivatives as orally active nonpeptide arginine vasopressin (AVP) V_2 receptor antagonists. After the lead structure OPC-31260 was structurally evaluated and optimized, the introduction of the 7-Cl moiety on the benzazepine and 2-CH_3 on the aminobenzoyl moiety enhanced its oral activity. The new AVP-V_2 selective antagonist OPC-41061 was determined to be a potent and orally active agent.

Introduction

Arginine vasopressin (AVP) is a well-known hormone that exerts its major actions through two well-defined receptor subtypes: the V_{1a} and V_2 receptors. AVP's primary roles involve the regulation of renal and cardiovascular functions. Through the kidney AVP-V_2 receptor, its antidiuretic actions correct fluctuations in blood osmolality, and through the vascular smooth muscle AVP-V_{1a} receptors, its pressor actions help maintain peripheral resistance under certain adverse conditions.[1–3] Since we reported a novel series of orally active, nonpeptide AVP-V_2 receptor antagonists (OPC-31260),[4,5] many similar structural types and one distinctly diverse V_2 receptor antagonist have been reported.[6–12]

Here we report some of our recent findings after enhancing the in vitro and in vivo activities using benzazepine as our template. Though the amino group at the 5-position seemed essential for oral bioavailability as described in the finding of OPC-31260,[4] the further modification of the amino moiety for the enhancement of the binding affinity failed (part **A** in Fig. 1). We then focused our studies on the effects of other additional substituents on the benzazepine skeleton (part **B**). These studies indicated that introducing a Cl[13] group at the 7-position enhanced the oral activity, the further optimization in combination with additional functional groups (part **C**) led to more potent antagonists than OPC-31260.

Chemistry

The syntheses of the Cl-substituted benzazepine-5-ones (**9a–d**) at positions 6 to 9 are shown in Schemes 1 and 2. The Cl-substituted 2-nitrobenzoic acids (**1a–c**) were converted to methylesters (**2a–c**) using dimethylsulfate and K_2CO_3 in acetone. The nitro group of **2a–c** was reduced with tin (II) chloride in ethanol to afford the anilines (**3a–c**). On the other hand, a 6-Cl derivative **3d** was prepared from the aminobenzoic acid **5** by treatment with thionyl chloride in methanol. Tosylation of **3a–d** with *p*-toluenesulfonylchloride in pyridine provided tosylamide (**4a–d**, Scheme 1). **4a–d** were reacted with ethyl 4-bromobutylate to give **6a–d**. The Dieckmann

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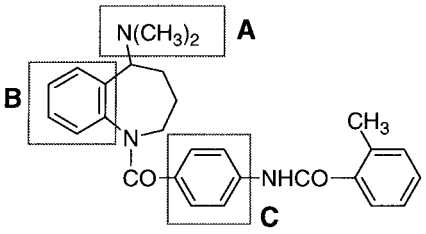
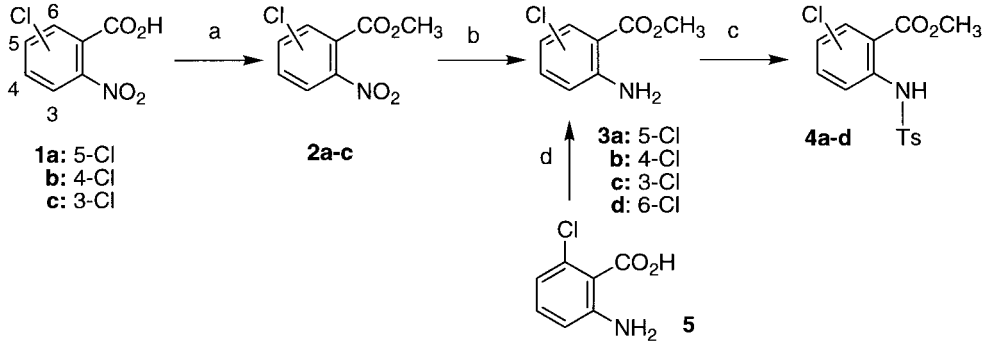
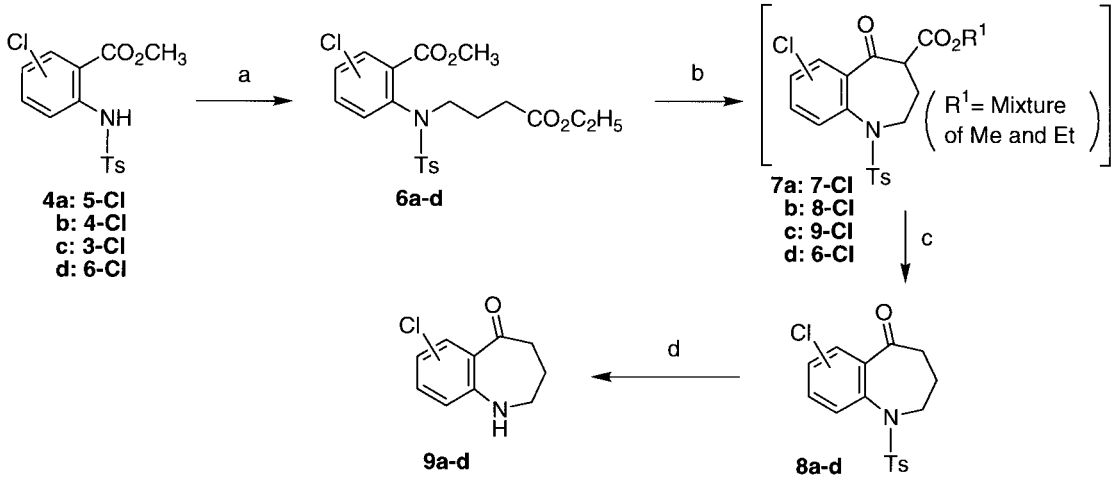


Figure 1.

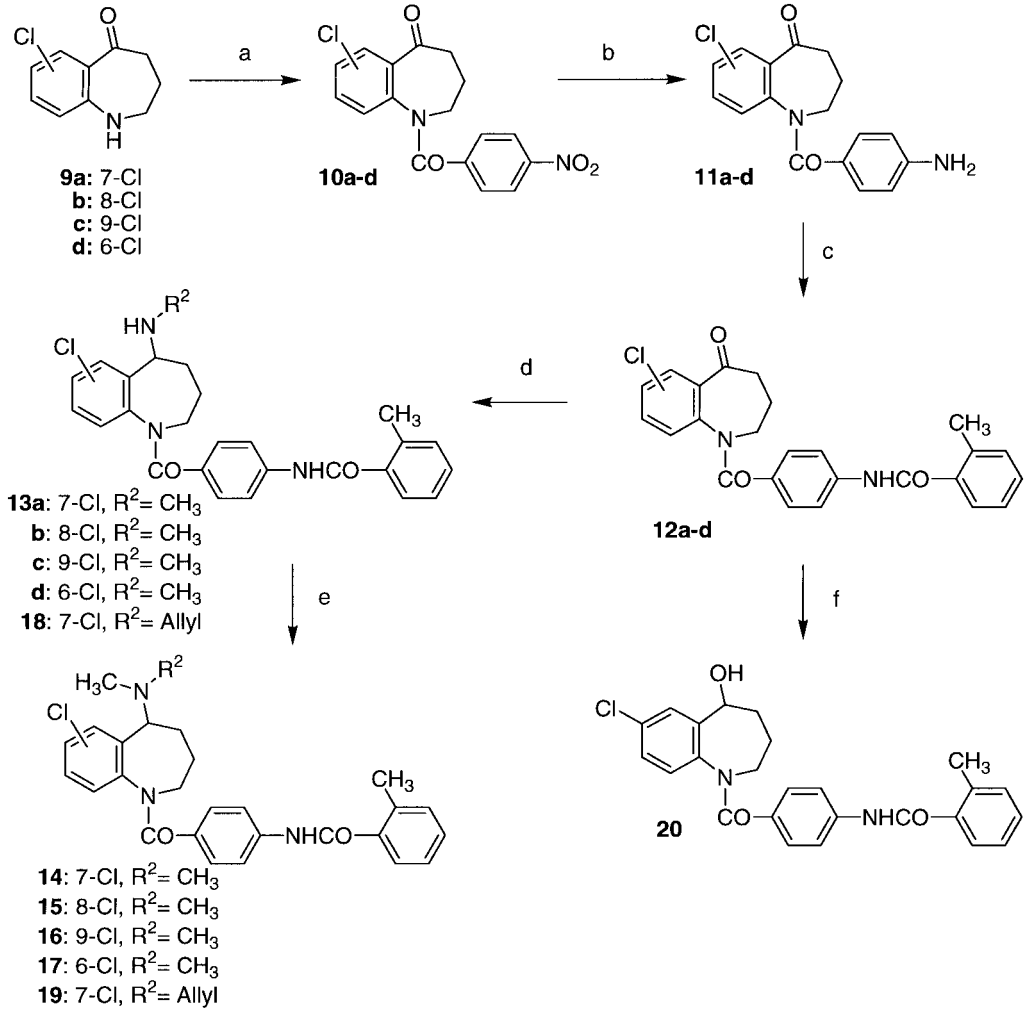
condensation of **6a–d** (heating with potassium *t*-butoxide in toluene) provided the benzazepinones (**7a–d**). **7a–d** were decarboxylated by heating with concentrated hydrochloric acid in acetic acid to give **8a–d**.[14] The key intermediates **9a–d** were obtained by deprotection of the tosylates (**8a–d**) by heating in polyphospholic acid (Scheme 2). The synthesis of the target compounds **14–22** are shown in Schemes 3 and 4. **9a–d** were reacted with 4-nitrobenzoyl chloride to give the amides (**10a–d**). The nitro group of **10a–d** was reduced by hydrogenation with PtO_2 in a mixture of concentrated hydrochloric acid and acetic acid. The condensation of the resultant aniline (**11a–d**) with 2-methylbenzoyl chloride produced the amides (**12a–d**). The 5-keto group was converted into an *N*,*N*-dimethylamino group in two steps because of the poor reactivity of the 5-keto group. The imine formation from **12a–d** with 30% CH_3NH_2 in methanol and molecular sieves 4A, followed by the reduction of the imino group with sodium borohydride afforded the monomethylamino derivatives (**13a–d**). The dimethylamino derivatives (**14–17**) were obtained by the reductive amination of **13a–d** with 37% formaldehyde and sodium cyanoborohydride in a mixture of acetic acid and methanol. The allylamino derivative **19** was synthesized from the 5-keto derivative **12a** by reductive amination with allylamine, followed by an additional methylation with formaldehyde. The 5-OH derivative **20** was obtained from **12a** by the reduction of the keto group with sodium borohydride in methanol (Scheme 3). The synthesis of the *O*-alkylated derivatives (**21, 22**) are shown in Scheme 4. The 5-keto group of **10a** was converted into OH by reduction with sodium borohydride in methanol to give **23**. The OH group was alkylated by treatment with sodium hydride in DMF, followed by the addition of iodomethane, to give the methylether (**24a**). The allylether (**24b**) was obtained in the same manner using allylbromide instead of iodomethane. The nitro group of **24a, b** was reduced with tin (II) chloride in ethanol. The resultant anilines (**25a, b**) were condensed with 2-methylbenzoyl chloride to provide **21** and **22**, respectively. The synthesis of **30–34** are shown in Scheme 5. **9a** was condensed with the 4-nitrobenzoic acid derivatives (**26a–e**)[15–18] to give the amides



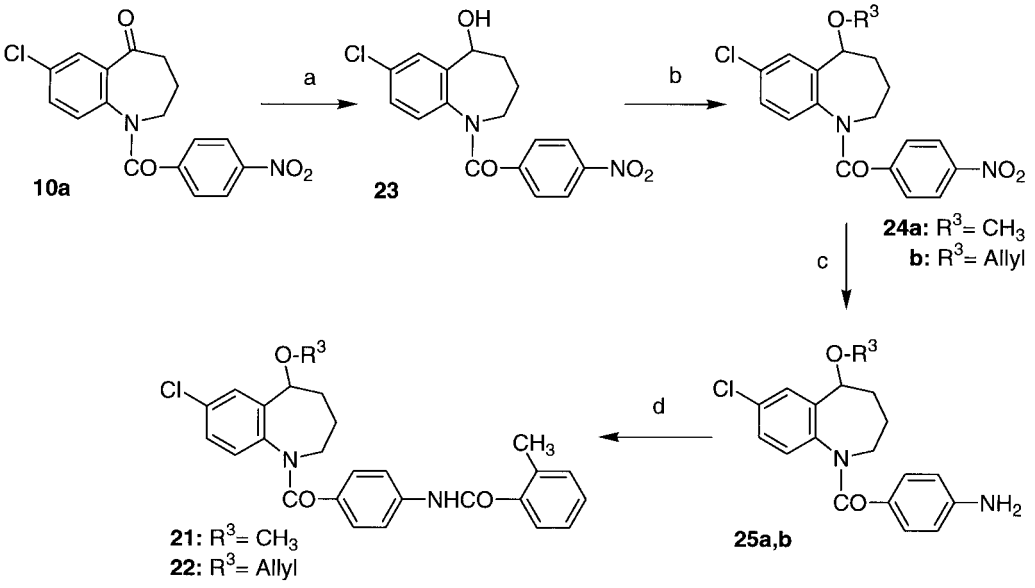
Scheme 1. *Reagents:* (a) Me_2SO_4, K_2CO_3, acetone; (b) $SnCl_2{\cdot}2H_2O$, EtOH, concd HCl; (c) *p*-TsCl, pyridine; (d) $SOCl_2$, MeOH.



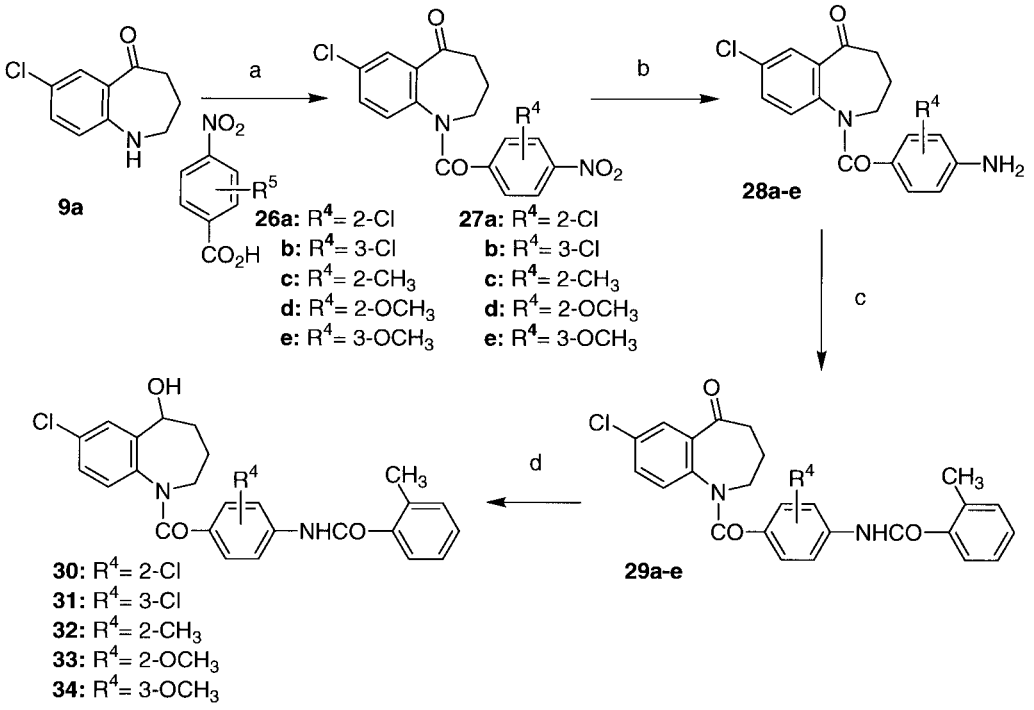
Scheme 2. *Reagents:* (a) ethyl 4-bromobutylate, K_2CO_3, DMF; (b) *t*-BuOK, toluene; (c) concd HCl, AcOH; (d) PPA.



Scheme 3. *Reagents:* (a) 4-nitrobenzoyl chloride, Et_3N, CH_2Cl_2 or pyridine; (b) H_2, PtO_2, concd HCl, AcOH; (c) 2-methylbenzoyl chloride, Et_3N or pyridine, CH_2Cl_2; (d) R^2NH_2, MS 4A, $NaBH_4$, MeOH; (e) 37% HCHO, $NaBH_3CN$, AcOH, MeOH; (f) $NaBH_4$, MeOH.



Scheme 4. *Reagents:* (a) $NaBH_4$, MeOH; (b) R^3-X, 60%NaH, DMF; (c) $SnCl_2{\cdot}2H_2O$, concd HCl, EtOH; (d) 2-methylbenzoyl chloride, Et_3N, CH_2Cl_2.



Scheme 5. *Reagents:* (a) $SOCl_2$, pyridine or Et_3N, CH_2Cl_2; (b) $SnCl_2{\cdot}2H_2O$, concd HCl, EtOH or H_2, PtO_2, concd HCl, AcOH; (c) 2-methylbenzoyl chloride, pyridine, CH_2Cl_2; (d) $NaBH_4$, MeOH.

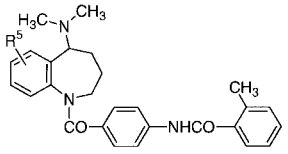
(**27a–e**). The nitro group was then reduced to provide the aniline derivatives (**28a–e**). **28a–e** were condensed again with 2-methylbenzoyl chloride to give the amides (**29a–e**). The subsequent reduction of the 5-keto moiety of **29a–e** with sodium borohydride lead to the target compounds (**30–34**).

Results and Discussion

The methods for the binding studies and in vivo studies are described in the Experimental. The results of the binding assay and in vivo studies are shown in Tables 1–3.

As shown in Table 1, the substitution of the Cl moiety at the 6 and 9 positions (**17**, **16**) lowered the affinity for the V_2 receptor by 16- and 11.6-fold compared to OPC-31260, respectively. The substitution at the 8-position (**15**) lowered the affinity by about fivefold. Interestingly, the binding affinity for the V_{1a} receptors was enhanced (7.4-fold) by the Cl-substitution at the 7 position (**14**) compared to OPC-31260. The diuretic activity after oral administration was enhanced by introducing a Cl atom at the 7-position compared to OPC-31260, as shown by the ED_3 values. We then focused again on the effects of substituents at the 5-position (as part **A**, Fig. 1) of the benzazepine ring and synthesized some derivatives (Table 2). It was clearly demonstrated that steric size was important for the V_2-affinity enhancement in the case of the amine derivatives. The monomethylamino derivative 13a was 3.6-fold more potent than dimethylamino derivative **14** for the V_2 receptor affinity. A longer chain (**18**) lowered the affinity compared with **13a**. Disubstitution (**19**) was negative for the binding affinity of the V_2 receptor. The steric effects of the hydroxy or alkoxy derivatives seemed smaller (**20, 21, 22**) compared to the amino series (**13a, 18**). It was not clear why there are differences in the binding affinity between the alkoxy and amino derivatives. The oral activity of **13a** and **18** was similar to **14**. We then decided to adopt the OH

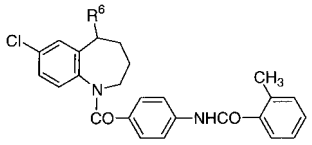
Table 1. Effects of a Cl-substituent on the benzazepine phenyl ring



Compound	R^5	Binding affinity[a] IC_{50} (μM) V_{1a}	V_2	Urine volume[b]	ED_3[c]
17	6-Cl	1.7	0.19	1.6	N.C.[d]
14	7-Cl	0.19	0.025	14.6	1.5
15	8-Cl	1.2	0.063	3.4	N.C.
16	9-Cl	0.54	0.14	2.4	N.C.
OPC-31260	H	1.4	0.012	12.3	3.8

[a] Compounds were tested for their ability to displace [^{3}H]-AVP at its specific binding sites in rat liver (V_{1a} receptors) and kidney (V_2 receptors) plasma membrane preparations (see Experimental).
[b] Urine volume values mean urine volume (mL) accumulated for 2 h when the test compounds were orally administered at a dose of 10 mg/kg.
[c] ED_3 represents the calculated dose (mg/kg, p.o.) required for a three fold increase in the 2 h urine volume compared to the control (see Experimental).
[d] Not calculated because of poor urine volume.

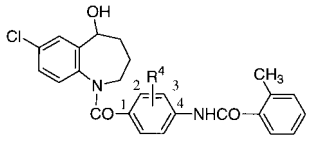
Table 2. Effects of substituents at the 5-position of the benzazepine ring



Compound	R^6	Binding affinity[a] IC_{50} (μM)		Urine volume[b]	ED_3[c]
		V_{1a}	V_2		
13a	NH-CH_3	0.064	0.007	15.5	1.4
18	NH-Allyl	0.045	0.018	15.4	3.3
19	N(CH_3)-Allyl	0.35	0.097	N.D.[e]	N.C.[d]
20	OH	0.017	0.003	7.2	N.C.[d]
21	O-CH_3	0.034	0.005	6.3	N.C.[d]
22	O-Allyl	0.053	0.009	7.6	N.C.[d]

[a–d] See Table 1.
[e] Not done because of the compound's poor affinity for the V_2 receptors.

Table 3. Effects of R^4 substituents on the phenyl ring of aminobenzoyl moiety



Compounds	R^4	Binding affinity[a] IC_{50} (μM)		Urine volume[b]	ED_3[c]
		V_{1a}	V_2		
30	2-Cl	0.29	0.008	16.8	1.6
31	3-Cl	0.031	0.028	3.0	N.C.[d]
32	2-CH_2	0.58	0.003	17.3	0.54
33	2-OCH_3	0.039	0.013	15.2	1.4
34	3-OCH_3	0.007	0.005	3.5	N.C.[d]

[a–d] See Table 1.

group as the substituent at the 5-position for further optimization because the OH derivative **20** showed the highest affinity for the V_2 receptor, although the oral activity and selectivity for the V_{1a} receptors did not improve compared to OPC-31260. The final optimization was carried out on the rest of the structure (as part **C**, Fig. 1, Table 3). The binding affinity for the V_2 receptors was slightly diminished by the 3-Cl (**31**) and 2-OCH_3 (**33**) substituents compared to **20**. Interestingly, the binding affinity for the V_{1a} receptors and oral activity (shown as urine volume) dramatically changed due to one substituent on the aminobenzoyl moiety (R^4). 2-Cl (**30**) and 2-CH_3 (**32**) substitutions lowered the affinity for the V_{1a} receptors but 3-OCH_3 (**34**) enhanced this affinity. As we previously reported on the V_{1a} selective nonpeptide antagonists, the binding affinity for the V_{1a} receptor was enhanced by one substituent that has hydrogen bonding ability.[19] Therefore, the enhancement by the 3-OCH_3 group might be explained in the same manner. The substitution at the 2-position enhanced the oral activity (**30, 32, 33**). Based on the result of better selectivity for the V_2 receptor toward V_{1a} receptor ($V_{1a}/V_2 = 193$) and potent oral activity ($ED_3 = 0.54$ mg/kg), compound **32** (OPC-41061) was selected for advanced in vivo studies and for clinical trials. Compound **32** also showed a very high affinity for human receptors (V_{1a}: $Ki = 12.3 \pm 0.8$ nM, V_2: $Ki = 0.43 \pm 0.06$ nM) as characterized in HeLa cells expressing cloned human AVP receptors.[20]

Conclusion

We described the development of the 5-OH benzazepine derivative OPC-41061 (**32**), a potent, orally active AVP V_2 antagonist. Although we previously reported the importance of the 5-amino group on the benzazepine ring for oral bioavailability, we discovered some compounds without the 5-amino moiety had the desired pharmacological properties by optimizing the additional functional groups and the combination with the functional groups on the structures. This finding seems very useful for optimizing by clinical necessity.

We hope that compound **32** (OPC-41061) may be useful for treating conditions characterized by water retention and the inappropriate secretion of AVP.

Experimental

Melting points were determined using a Yanagimoto Micro Point Apparatus and were uncorrected. ^{1}H NMR spectra were recorded on a Bruker AC-200 (200 MHz) spectrometer using tetramethylsilane (TMS) or 3-(trimethylsilyl)propionic acid-d_5 (TSP) as an internal standard. Elemental analyses were determined with a Yanaco MT-5 CHN Corder. Mass spectra were measured on a Varian MAT-312 instrument. All compounds were routinely checked by TLC on Merck Silica gel 60 F_{254} precoated plates. Chromatography refers to flash chromatography using E. Merck Kieselgel 60, 230–400 mesh silica gel. All materials were commercially available unless noted otherwise.

Methyl 5-chloro-2-nitrobenzoate (2a). To a mixture of 5-chloro-2-nitrobenzoic acid (**1a**, 15 g, 74.4 mmol) and K_2CO_3 (15.4 g, 111 mmol) was added Me_2SO_4 (9.2 mL, 97 mmol). The mixture was heated at reflux for 30 min. The mixture was poured into ice-aqueous ammonia and extracted with Et_2O. The organic layer was separated, washed with H_2O then dried over $MgSO_4$. The concentrated residue was purified by silica gel column chromatography (eluent, CH_2Cl_2) to give **2a** (16.4 g, quant.) as yellow oil: ^{1}H NMR ($CDCl_3$) δ 3.94 (3H, s), 7.57 (1H, dd, $J = 8.6$, 2.2 Hz), 7.69 (1H, d, $J = 2.2$ Hz), 7.92 (1H, d, $J = 8.6$ Hz).

Methyl 4-chloro-2-nitrobenzoate (2b). Using the same procedure as **2a**, 4-chloro-2-nitrobenzoic acid (**1b**, 25 g, 0.124 mol) was converted to ester **2b** (30 g, quant.): ^{1}H NMR ($CDCl_3$) δ 3.92 (3H, s), 7.64 (1H, dd, $J = 8.3$, 2.0 Hz), 7.74 (1H, d, $J = 8.3$ Hz), 7.87 (1H, d, $J = 2.0$ Hz).

Methyl 3-chloro-2-nitrobenzoate (2c). Using the same procedure as **2a**, 3-chloro-2-nitrobenzoic acid (**1c**, 19 g, 94 mmol) was converted to ester **2c** (18 g, 89%): ^{1}H NMR ($CDCl_3$) δ 3.92 (3H, s), 7.54 (1H, dd, J = 8.1, 7.8 Hz), 7.72 (1H, dd, J = 8.1, 1.4 Hz), 7.99 (1H, dd, J = 7.8, 1.4 Hz).

Methyl 2-amino-5-chlorobenzoate (3a). [21] To a mixture of **2a** (16.4 g, 76 mmol) in conc. HCl (70 mL) and EtOH (35 mL) was added dropwise a solution of $SnCl_2{\cdot}2H_2O$ (51.5 g, 228 mmol) in EtOH (70 mL). After the addition was completed, the mixture was stirred overnight at room temperature. The mixture was poured into ice-water, and pH value was adjusted to 8–9 by the addition of aqueous NaOH, then extracted with CH_2Cl_2. Insoluble material was removed through Celite layer, and the organic layer was separated, dried over $MgSO_4$, and concentrated to give **3a** (12.6 g, 89%) as crude oil: ^{1}H NMR ($CDCl_3$) δ 3.87 (3H, s), 5.30 (2H, brs), 6.60 (1H, d, J = 8.8 Hz), 7.20 (1H, dd, J = 8.8, 2.6 Hz), 7.81 (1H, d, J = 2.6 Hz).

Methyl 2-amino-4-chlorobenzoate (3b). [21] Using the same procedure as **3a, 3b** (22 g, 88%) was obtained as crude oil from **2b** (30 g, 0.139 mol): ^{1}H NMR ($CDCl_3$) δ 3.86 (3H, s), 5.80 (2H, brs), 6.60 (1H, dd, J = 8.5, 1.9 Hz), 6.66 (1H, d, J = 1.9 Hz), 7.78 (1H, d, J = 8.5 Hz).

Methyl 2-amino-3-chlorobenzoate (3c). Using the same procedure as **3a**, **3c** (9.9 g, 96%) was obtained as crude oil from **2c** (12 g, 55.7 mmol): ^{1}H NMR ($CDCl_3$) δ 3.88 (3H, s), 6.27 (2H, brs), 6.58 (1H, dd, J = 8.0, 7.7 Hz), 7.40 (1H, dd, J = 7.7, 1.4 Hz), 7.80 (1H, dd, J = 8.0, 1.4 Hz).

Methyl 2-amino-6-chlorobenzoate (3d). A mixture of 2-amino-6-chlorobenzoic acid (**5**, 23 g, 0.134 mol) and $SOCl_2$ (200 mL) was heated at reflux for 2 h. After the mixture was concentrated under reduced pressure, MeOH (300 mL) was added at 0–5°C. The mixture thus obtained was heated at reflux for 1 h, and concentrated under reduced pressure. The residue was diluted with CH_2Cl_2, the pH value was adjusted to about 7 by adding dil aq NaOH. The organic layer was separated and dried over $MgSO_4$. The residue was purified by silica gel column chromatography (eluent, *n*-hexane:AcOEt (4:1)) to give **3d** (20.2 g, 81%) as brown oil: ^{1}H NMR ($CDCl_3$) δ 3.93 (3H, s), 4.74 (2H, brs), 6.57 (1H, d, J = 8.3 Hz), 6.74 (1H, d, J = 7.8 Hz), 7.08 (1H, dd, J = 8.3, 7.8 Hz).

Methyl 5-chloro-2-(*N*-*p*-toluenesulfonyl)aminobenzoate (4a). To a mixture of **3a** (12.6 g, 67.9 mmol) in pyridine (60 mL) was added *p*-TsCl (15.5 g, 81.3 mmol). The mixture was stirred overnight at room temperature. The mixture was poured into ice-water, and the resultant precipitates were collected by filtration. The filtrates were dissolved in CH_2Cl_2, and the solution was washed with dil. HCl, H_2O, and dried over $MgSO_4$. The residue thus obtained was purified by silica gel column chromatography (eluent, *n*-hexane:AcOEt (4:1)) to give **4a** (19.5 g, 85%) as yellow powder: ^{1}H NMR ($CDCl_3$) δ 2.37 (3H, s), 3.88 (3H, s), 7.23 (2H, d, J = 8.4 Hz), 7.40 (1H, dd, J = 8.8, 2.6 Hz), 7.62–7.78 (3H, m), 7.88 (1H, d, J = 2.6 Hz), 10.50 (1H, brs).

Methyl 4-chloro-2-(*N*-*p*-toluenesulfonyl)aminobenzoate (4b). [22] Using the same procedure as **4a**, **4b** (36.6 g, 95%) was obtained from **3b** (21 g, 113 mmol) as yellow powder: ^{1}H NMR ($CDCl_3$) δ 2.38 (3H, s), 3.88 (3H, s), 7.00 (1H, dd, J = 8.6, 2.0 Hz), 7.26 (2H, d, J = 8.2 Hz), 7.72 (1H, d, J = 2.0 Hz), 7.77 (2H, d, J = 8.2 Hz), 7.85 (1H, d, J = 8.6 Hz), 10.73 (1H, brs).

Methyl 3-chloro-2-(*N*-*p*-toluenesulfonyl)aminobenzoate (4c). Using the same procedure as **4a, 4c** (5.1 g, 23%) was obtained from **3c** (12.3 g, 66 mmol) as yellow powder: ^{1}H NMR ($CDCl_3$) δ 2.41 (3H, s), 3.66 (3H, s), 7.14–7.33 (3H, m), 7.53 (2H, d, J = 8.3 Hz), 7.60 (1H, dd, J = 7.9, 1.5 Hz), 7.70 (1H, dd, J = 7.9, 1.5 Hz), 8.27 (1H, brs).

Methyl 6-chloro-2-(*N*-*p*-toluenesulfonyl)aminobenzoate (4d). Using the same procedure as **4a, 4d** (34 g, 92%) was obtained from **3d** (20.2 g, 109 mmol) as yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.39 (3H, s), 3.74 (3H, s), 7.12–7.41 (4H, m), 7.55–7.66 (2H, m), 7.81–7.92 (1H, m), 8.39 (1H, brs).

Methyl 5-chloro-2-[*N*-(3-ethoxycarbonyl)propyl-*N*-*p*-toluenesulfonyl]aminobenzoate (6a). A mixture of **4a** (19.5 g, 57.4 mmol), ethyl 4-bromobutylate (12.3 g, 63 mmol), and K_2CO_3 (22.2 g, 160.6 mmol) in DMF (140 mL) was heated at 120°C for 4 h. After the reaction was completed, the mixture was poured into ice-water, then extracted with AcOEt. The organic layer was separated, washed with water, and dried over $MgSO_4$. The residue was purified by silica gel column chromatography (eluent, *n*-hexane:AcOEt- (3:1)) to give **6a** (24.5 g, 94%) as white powder: ^{1}H NMR ($CDCl_3$) δ 1.23 (3H, t, J = 7.2 Hz), 1.85 (2H, quint., J = 7.2 Hz), 2.33–2.56 (4H, m), 3.36–3.92 (2H, m), 3.83 (3H, s), 4.09 (2H, q, J = 7.2 Hz), 6.84 (1H, d, J = 8.6 Hz), 7.18–7.53 (5H, m), 7.84 (1H, d, J = 2.6 Hz).

Methyl 4-chloro-2-[*N*-(3-ethoxycarbonyl)propyl-*N*-*p*-toluenesulfonyl]aminobenzoate (6b). Using the same procedure as **6a, 6b** (53.6 g, quant.) was obtained from **4b** (36.4 g, 107 mmol): ^{1}H NMR ($CDCl_3$) δ 1.23 (3H, t, J = 7.1 Hz), 1.87 (2H, quint., J = 7.1 Hz), 2.32–2.56 (5H, m), 3.32–3.93 (2H, m), 3.83 (3H, s), 4.10 (2H, q, J = 7.1 Hz), 6.88 (1H, d, J = 2.0 Hz), 7.27 (2H, d, J = 8.0 Hz), 7.37 (1H, dd, J = 8.5, 2.0 Hz), 7.46 (2H, d, J = 8.0 Hz), 7.83 (1H, d, J = 8.5 Hz).

Methyl 3-chloro-2-[*N*-(3-ethoxycarbonyl)propyl-*N*-*p*-toluenesulfonyl]aminobenzoate (6c). Using the same procedure as **6a, 6c** (13.4 g, quant.) was obtained from **4c** (10 g, 29.5 mmol): ^{1}H NMR ($CDCl_3$) δ 1.22 (3H, t, J = 7.1 Hz), 1.85–2.24 (2H, m), 2.35 (2H, t, J = 7.2 Hz), 2.41 (3H, s), 3.61–3.94 (2H, m), 3.82 (3H, s), 4.10 (2H, q, J = 7.1 Hz), 7.18–7.42 (3H, m), 7.45–7.63 (3H, m), 7.77 (1H, dd, J = 7.6, 1.7 Hz).

Methyl 6-chloro-2-[*N*-(3-ethoxycarbonyl)propyl-*N*-*p*-toluenesulfonyl]aminobenzoate (6d). Using the same procedure as **6a, 6d** (45.8 g, quant.) was obtained from **4d** (34 g, 100 mmol) as yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.23 (3H, t, J = 7.1 Hz), 1.79 (2H, quint., J = 7.3 Hz), 2.33 (2H, t, J = 7.1 Hz), 2.44 (3H, s), 3.25–3.72 (2H, m),

3.89 (3H, s), 4.10 (2H, q, $J=7.1$ Hz), 6.73–6.85 (1H, m), 7.15–7.43 (4H, m), 7.53–7.67 (2H, m).

7-Chloro-5-oxo-2,3,4,5-tetrahydro-1-*p*-toluenesulfonyl-1*H*-1-benzazepine (8a). To a heated mixture of *t*-BuOK (12.1 g, 108 mmol) in toluene (400 mL) at 70°C was added portionwise **6a** (24.5 g, 54 mmol). After the addition was completed, the mixture was heated at reflux for 30 min. The mixture was cooled to room temperature then poured into ice-water. The extraction with CH_2Cl_2 was successively done, and the organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to afford crude **7a** (18.4 g) as a mixture of Me and Et esters. To the mixture **(7a)** thus obtained, were added AcOH (90 mL), conc. HCl (30 mL) and H_2O (9 mL). The mixture was heated at reflux for 5 h and poured into ice-water. The pH value was adjusted to about 7–8 by adding dil aq NaOH. The mixture was extracted with CH_2Cl_2. The organic layer was separated, dried over $MgSO_4$, concentrated, and purified by silica gel column chromatography (eluent, *n*-hexane:AcOEt (4:1)) to give **8a** (11.4 g, 60%) as white powder: ^{1}H NMR ($CDCl_3$) δ 1.86–2.05 (2H, m), 2.27–2.52 (2H, m), 2.43 (3H, s), 3.84 (2H, t, $J=6.5$ Hz), 7.20–7.63 (6H, m), 7.67 (1H, d, $J=2.2$ Hz).

8-Chloro-5-oxo-2,3,4,5-tetrahydro-1-*p*-toluenesulfonyl-1*H*-1-benzazepine (8b). Using the same procedure as **8a, 8b** (19.5g, 51%) was obtained from **6b** (53.6 g, 118 mmol): ^{1}H NMR ($CDCl_3$) δ 1.87–2.01 (2H, m), 2.31–2.53 (2H, m), 2.44 (3H, s), 3.84 (2H, t, $J=6.5$ Hz), 7.19–7.42 (3H, m), 7.51 (1H, d, $J=1.9$ Hz), 7.57–7.76 (3H, m).

9-Chloro-5-oxo-2,3,4,5-tetrahydro-1-*p*-toluenesulfonyl-1*H*-1-benzazepine (8c). Using the same procedure as **8a, 8c** (5.8 g, 59%) was obtained from **6c** (12.8 g, 28.3 mmol): ^{1}H NMR ($CDCl_3$) δ 1.42–2.01 (3H, m), 2.23–2.52 (1H, m), 2.44 (3H, s), 3.52–3.73 (1H, m), 3.77–4.05 (1H, m), 7.18–7.73 (7H, m).

6-Chloro-5-oxo-2,3,4,5-tetrahydro-1-*p*-toluenesulfonyl-1*H*-1-benzazepine (8d). Using the same procedure as **8a, 8d** (3.5 g, 14%) was obtained from **6d** (32.5 g, 71.7 mmol): ^{1}H NMR ($CDCl_3$) δ 1.74–1.93 (2H, m), 2.28–2.52 (2H, m), 2.43 (3H, s), 3.73 (2H, t, $J=6.1$ Hz), 7.21–7.48 (5H, m), 7.49–7.63 (2H, m); MS (ES) m/z 349 $[M]^+$.

7-Chloro-5-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine (9a). To preheated polyphospholic acid (PPA, 30 g) at 80–100°C was added **8a** (4.4 g, 12.6 mmol). The mixture was stirred for 1.5 h at the same temperature, then poured into ice-water. After the pH value was adjusted to about 8–9 by adding aq NaOH, the mixture was extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), and concentrated. The residue was purified by silica gel column chromatography (eluent, *n*-hexane: AcOEt (3:1)) to give **9a** (2 g, 81%) as yellow powder: ^{1}H NMR ($CDCl_3$) δ 2.17 (2H, quint., $J=7.0$ Hz), 2.82 (2H, t, $J=7.2$ Hz), 3.13–3.32 (2H, m), 4.71 (1H, brs), 6.70 (1H, d, $J=8.6$ Hz), 7.17 (1H, dd, $J=8.6$, 2.6 Hz), 7.67 (1H, d, $J=2.6$ Hz).

8-Chloro-5-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine (9b). Using the same procedure as **9a, 9b** (9 g, 82%) was obtained from **8b** (19.5 g, 55.8 mmol): ^{1}H NMR ($CDCl_3$) δ 2.17 (2H, quint. $J=6.9$ Hz), 2.81 (2H, t, $J=7.2$ Hz), 3.12–3.35 (2H, m), 4.65 (1H, brs), 6.65–6.86 (2H, m), 7.64 (1H, d, $J=9.1$ Hz).

9-Chloro-5-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine (9c). Using the same procedure as **9a, 9c** (2.73 g, 84%) was obtained from **8c** (5.8 g, 16.6 mmol) as brown powder: ^{1}H NMR ($CDCl_3$) δ 2.24 (2H, quint., $J=7.2$ Hz), 2.83 (2H, t, $J=7.3$ Hz), 3.20–3.42 (2H, m), 5.40 (1H, brs), 6.74 (1H, dd, $J=7.8$, 7.8 Hz), 7.37 (1H, dd, $J=7.8$, 1.5 Hz), 7.61 (1H, dd, $J=7.8$, 1.5 Hz).

6-Chloro-5-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine (9d). Using the same procedure as **9a, 9d** (1.7 g, 95%) was obtained from **8d** (3.2 g, 9.2 mmol): ^{1}H NMR ($CDCl_3$) δ 2.16 (2H, quint., $J=6.8$ Hz), 2.82 (2H, t, $J=7.2$ Hz), 3.12–3.36 (2H, m), 4.77 (1H, brs), 6.62 (1H, dd, $J=8.1$, 1.0 Hz), 6.79 (1H, dd, $J=7.8$, 1.0 Hz), 7.04 (1H, dd, $J=8.1$, 7.8 Hz).

7-Chloro-1-(4-nitrobenzoyl)-5-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine (10a). To a mixture of **9a** (2 g, 10.2 mmol) and Et_3N (1.6 g, 15.8 mmol) in CH_2Cl_2 (50 mL) was added 4-nitrobenzoyl chloride (2.3 g, 12.4 mmol) at room temperature. The mixture was stirred for 2 h, poured into H_2O, then extracted with CH_2Cl_2. The organic layer was separated, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography (eluent, *n*-hexane:AcOEt (2:1)) to afford **10a** (2 g, 57%) as white powder: mp. 157.5–159.5°C; ^{1}H NMR ($CDCl_3$) δ 1.85–2.45 (2H, m), 2.91 (2H, t, $J=6.2$ Hz), 2.72–5.28 (2H, m), 6.52–6.74 (1H, m), 7.10–7.52 (3H, m), 7.82 (1H, d, $J=2.5$ Hz), 8.09 (2H, d, $J=8.6$ Hz).

8-Chloro-1-(4-nitrobenzoyl)-5-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine (10b). Using the same procedure as **10a, 10b** (8.4 g, 95%) was obtained from **9b** (5 g, 25.6 mmol) as yellow powder: mp. 151.5–153.5°C; ^{1}H NMR ($CDCl_3$) δ 1.86–2.42 (2H, m), 2.90 (2H, t, $J=6.3$ Hz), 3.12–5.23 (2H, m), 6.58–6.86 (1H, m), 7.18–7.53 (3H, m), 7.82 (1H, d, $J=8.4$ Hz), 8.10 (2H, d, $J=8.7$ Hz).

9-Chloro-1-(4-nitrobenzoyl)-5-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine (10c). To a solution of **9c** (2.7 g, 13.8 mmol) in pyridine (20 mL) was added 4-nitrobenzoyl chloride (3.07 g, 16.5 mmol) at room temperature. The mixture was heated at 50°C for 1 h, poured into H_2O, then extracted with CH_2Cl_2. The organic layer was washed with dil HCl, water, dried over $MgSO_4$, and concentrated. The purification by silica gel column chromatography (eluent, *n*-hexane:AcOEt (2:1)) of the residue was not succeeded. Therefore the obtained mixture was used as **10c** (2.5 g, yellow amorphous solid) for next step.

6-Chloro-1-(4-nitrobenzoyl)-5-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine (10d). Using the same procedure as **10a, 10d** (2.43 g, 92%) was obtained from **9d** (1.5 g, 7.7 mmol) as white powder: mp. 198–202°C; ^{1}H NMR ($CDCl_3$) δ 1.85–2.34 (2H, m), 2.72–2.91 (2H, m), 3.18–3.56 (1H, m), 4.44–4.83 (1H, m), 6.58 (1H, d, $J=$

7.7 Hz), 7.02–7.17 (1H, m), 7.23–7.45 (3H, m), 7.96–8.16 (2H, m).

1-(4-Aminobenzoyl)-7-chloro-5-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine (11a). A mixture of **10a** (2 g, 5.8 mmol), PtO_2 (0.2 g), and conc HCl (0.6 mL) in AcOH (30 mL) was stirred under H_2 atmosphere at 1 atm. After 390 mL of H_2 was absorbed, PtO_2 was removed by filtration, and filtrate was concentrated under reduced pressure. The residue was dissolved in $CHCl_3$, washed with aq $NaHCO_3$, dried ($MgSO_4$), and concentrated. The residue thus obtained was purified by silica gel column chromatography (eluent, CH_2Cl_2:MeOH (9:1)) to give **11a** (1.2 g, 66%) as white powder: mp. 193–193.5°C; ^{1}H NMR ($CDCl_3$) δ 2.02–2.28 (2H,m), 2.89 (2H, t, J = 6.4 Hz), 3.55–4.45 (4H, m), 6.37–6.52 (2H, m), 6.71 (1H, d, J = 8.5 Hz), 7.01–7.13 (2H, m), 7.19 (1H, dd, J = 8.5, 2.6 Hz), 7.84 (1H, d, J = 2.6 Hz).

1-(4-Aminobenzoyl)-8-chloro-5-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine (11b). Using the same procedure as **11a, 11b** (3.7 g, 51%) was obtained from **10b** (8 g, 23.2 mmol) as white powder: mp. 171–174°C; ^{1}H NMR ($CDCl_3$) δ 2.01–2.26 (2H, m), 2.77–2.97 (2H, m), 3.37–4.44 (4H, m), 6.32–6.53 (2H, m), 6.78 (1H, d, J = 2.0 Hz), 6.96–7.22 (2H, m), 7.21 (1H, dd, J = 8.4, 2.0 Hz), 7.83 (1H, d, J = 8.4 Hz).

1-(4-Aminobenzoyl)-9-chloro-5-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine (11c). Using the same procedure as **11a, 11c** (0.53 g, 10% from **9c**) was obtained from **10c** (2.5 g) as yellow powder: mp. 192.5–195°C; ^{1}H NMR ($CDCl_3$) δ 1.61–1.98 (1H, m), 2.06–2.34 (1H, m), 2.53–2.93 (2H, m), 3.16–3.43 (1H, m), 3.53–4.05 (2H, m), 4.51–4.83 (1H, m), 6.35 (2H, d, J = 8.5 Hz), 7.03 (2H, d, J = 8.5 Hz), 7.18–7.71 (3H, m); MS (ES) m/z 314 $[M]^+$.

1-(4-Aminobenzoyl)-6-chloro-5-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine (11d). Using the same procedure as **11a, 11d** (1.54 g, 73%) was obtained from **10d** (2.3 g, 6.7 mmol) as white powder: mp. 166–169°C; ^{1}H NMR ($CDCl_3$) δ 1.92–2.21 (2H, m), 2.66–2.87 (2H, m), 3.28–4.87 (4H, m), 6.42 (2H, d, J = 8.4 Hz), 6.61 (1H, d, J = 7.9 Hz), 6.97–7.20 (3H, m), 7.29 (1H, d, J = 7.9 Hz).

7-Chloro-1-[4-[(2-methylbenzoyl)amino]benzoyl]-5-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine (12a). To a mixture of **11a** (0.5 g, 1.6 mmol) and Et_3N (0.24 g, 2.4 mmol) in CH_2Cl_2 (10 mL), was added 2-methylbenzoyl chloride (0.3 g, 1.9 mmol) at room temperature. After being stirred for 1.5 h at room temperature, the mixture was poured into H_2O and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (eluent, CH_2Cl_2:MeOH (100:1)) to provide **12a** (0.75 g, quant.) as white powder: mp. 185.5–186°C; ^{1}H NMR ($CDCl_3$) δ 1.93–2.33 (2H, m), 2.47 (3H, s), 2.89 (2H, t, J = 6.3 Hz), 3.13–4.92 (2H, m), 6.69 (1H, d, J = 8.5 Hz), 7.16–7.61 (9H, m), 7.72 (1H, brs), 7.83 (1H, d, J = 2.5 Hz).

8-Chloro-1-[4-[(2-methylbenzoyl)amino]benzoyl]-5-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine (12b). Using the same procedure as **12a, 12b** (1.65 g, quant.) was obtained from **11b** (1.2 g, 3.8 mmol) as white powder: mp. 212.5–215°C; ^{1}H NMR ($CDCl_3$) δ 2.00–2.32 (2H, m), 2.47 (3H, s), 2.78–2.97 (2H, m), 3.32–4.74 (2H, m), 6.79 (1H, d, J = 1.8 Hz), 7.13–7.64 (9H, m), 7.73 (1H, brs), 7.83 (1H, d, J = 8.4 Hz).

9-Chloro-1-[4-[(2-methylbenzoyl)amino]benzoyl]-5-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine (12c). Using the same procedure as **12a, 12c** (0.6 g, quant.) was obtained from **11c** (0.45 g, 1.2 mmol) as a pink amorphous compound: ^{1}H NMR ($CDCl_3$) δ 1.68–1.97 (1H, m), 2.13–2.35 (1H, m), 2.45 (3H, s), 2.65–2.94 (2H, m), 3.25–3.43 (1H, m), 4.53–4.83 (1H, m), 7.10–7.82 (12H, m).

6-Chloro-1-[4-[(2-methylbenzoyl)amino]benzoyl]-5-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine (12d). Using the same procedure as **12a, 12d** (0.85 g, 52%) was obtained from **11d** (0.7 g, 2.2 mmol) as white powder: mp. 196.5–197°C; ^{1}H NMR ($CDCl_3$) δ 1.90–2.25 (2H, m), 2.45 (3H, s), 2.66–2.85 (2H, m), 3.08–3.75 (1H, m), 4.06–4.84 (1H, m), 6.61 (1H, d, J = 7.1 Hz), 7.05–7.53 (10H, m), 7.71 (1H, brs).

7-Chloro-5-(*N*-methylamino)-1-[4-[(2-methylbenzoyl)-amino]benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine (13a). A mixture of **12a** (0.75 g, 1.7 mmol), methylamine (30% solution in MeOH, 7.5 mL), and MS 4A (1.5 g) in MeOH (30 mL) was heated at reflux for 6 h. After cooling to room temperature, $NaBH_4$ (0.1 g, 2.6 mmol) was added. The mixture was stirred overnight at room temperature, then insoluble materials were removed by filtration. The filtrate thus obtained was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2, washed with H_2O, dried ($MgSO_4$), and concentrated. The residue was purified by silica gel column chromatography (eluent, CH_2Cl_2:MeOH (100:1)) to give **13a** (0.62 g, 80%) as white powder: ^{1}H NMR ($CDCl_3$) δ 1.30–2.72 (5H, m), 2.48 (3H, s), 2.55 (3H, s), 2.87–5.23 (3H, m), 6.46–6.65 (1H, m), 6.88–7.03 (1H, m), 7.08–7.63 (10H, m); MS (ES) m/z 447 $[M]^+$. Anal. calcd for $C_{26}H_{26}ClN_3O_2 \cdot 0.4H_2O$: C, 68.61; H, 5.93; N, 9.23; found C, 68.77; H, 6.16; N, 8.82.

8-Chloro-5-(*N*-methylamino)-1-[4-[(2-methylbenzoyl)-amino]benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine (13b). Using the same procedure as **13a, 13b** (0.8 g, 78%) was obtained from **12b** (1 g, 2.3 mmol) as white powder: mp. 192–194.5°C; ^{1}H NMR ($CDCl_3$) δ 1.27–2.66 (5H, m), 2.46 (3H, s), 2.53 (3H, s), 2.83–5.23 (3H, m), 6.55–6.73 (1H, m), 6.96–7.55 (10H, m), 7.61–7.84 (1H, m). Anal. calcd for $C_{26}H_{26}ClN_3O_2 \cdot 0.6H_2O$: C, 68.07; H, 5.98; N, 9.16; found C, 67.89; H, 5.77; N, 9.05.

9-Chloro-5-(*N*-methylamino)-1-[4-[(2-methylbenzoyl)-amino]benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine (13c). Using the same procedure as **13a, 13c** (0.4 g, 64%) was obtained from **12c** (0.6 g, 1.4 mmol) as white powder: mp. 186–189°C; ^{1}H NMR ($CDCl_3$) δ 1.33–2.70 (5H, m), 2.46 (3H, s), 2.57 (3H, s), 2.93–5.20 (3H, m), 7.07–7.78 (12H, m); MS (ES) m/z 447 $[M]^+$. Anal. calcd for $C_{26}H_{26}ClN_3O_2$: C, 69.71; H, 5.85; N, 9.38; found C, 69.35; H, 5.85; N, 9.37.

6-Chloro-5-(*N*-methylamino)-1-[4-[(2-methylbenzoyl)-amino]benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine (13d). Using the same procedure as **13a**, crude product of **13d** (0.3 g) was obtained from **12d** (0.75 g, 1.7 mmol) as colorless amorphous solid, and that was used without further purification.

5-(*N*-Allylamino)-7-chloro-1-[4-[(2-methylbenzoyl)amino]-benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine (18). Using the same procedure as **13a, 18** (0.64 g, 49%) was obtained from **12a** (1.2 g, 2.8 mmol) by using allylamine instead of methylamine as white powder: mp. 180–181.5°C; ^{1}H NMR ($CDCl_3$) δ 1.33–2.83 (5H, m), 2.47 (3H, s), 2.96–4.62 (5H, m), 5.03–5.34 (2H, m), 5.77–6.13 (1H, m), 6.56 (1H, d, J = 8.2 Hz), 6.87–7.03 (1H, m), 7.12–7.68 (10H, m). Anal. calcd for $C_{28}H_{28}ClN_3O_2$: C, 70.95; H, 5.95; N, 8.87; found C, 70.70; H, 5.80; N, 8.77.

7-Chloro-5-(*N*,*N*-dimethylamino)-1-[4-[(2-methylbenzoyl)-amino]benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine (14). To a mixture of **13a** (0.15 g, 0.34 mmol), formalin (37% aqueous solution, 0.2 mL), and $NaBH_3CN$ (30 mg, 0.48 mmol) in MeOH (2 mL), was added AcOH (0.15 mL) at 5–10°C. After being stirred for 1 h at room temperature, the mixture was poured into aq K_2CO_3 and ice mixture, extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (eluent, CH_2Cl_2:MeOH (100:1)) to give **14** (97 mg, 61%) as white powder: mp. 212–214°C; ^{1}H NMR ($CDCl_3$) δ 1.07–2.54 (4H, m), 2.41 (6H, s), 2.48 (3H, s), 2.92–3.52 (3H, m), 3.90–4.18 (1H, m), 6.87–7.02 (1H, m), 7.12–7.67 (10H, m); MS (ES) m/z 461 $[M]^+$. Anal. calcd for $C_{27}H_{28}ClN_3O_2$: C, 70.20; H, 6.11; N, 9.10; found C, 70.16; H, 6.25; N, 9.04.

8-Chloro-5-(*N*,*N*-dimethylamino)-1-[4-[(2-methylbenzoyl)-amino]benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine (15). Using the same procedure as **14, 15** (0.27 g, 57%) was obtained from **13b** (0.45 g, 1 mmol) as white powder: mp. 175–177°C; ^{1}H NMR ($CDCl_3$) δ 1.07–2.85 (4H, m), 2.40 (6H, s), 2.48 (3H, s), 2.94–3.68 (2H, m), 3.88–5.25 (1H,m), 6.53–6.73 (1H, m), 6.95–7.73 (11H, m); MS (ES) m/z 461 $[M]^+$. Anal. calcd for $C_{27}H_{28}ClN_3O_2$: C, 70.20; H, 6.11; N, 9.10; found C, 70.17; H, 5.88; N, 9.09.

9-Chloro-5-(*N*,*N*-dimethylamino)-1-[4-[(2-methylbenzoyl)-amino]benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine (16). Using the same procedure as **14, 16** (0.19 g, 80%) was obtained from **13c** (0.23 g, 0.51 mmol) as white powder: mp. 218–220°C; ^{1}H NMR ($CDCl_3$) δ 1.05–1.55 (2H, m), 1.75–2.25 (2H, m), 2.44 (6H, s), 2.46 (3H, s), 3.32–3.50 (1H, m), 3.62–3.78 (1H, m), 4.02–4.22 (1H, m), 7.08–7.76 (12H, m); MS (ES) m/z 461 $[M]^+$. Anal. calcd for $C_{27}H_{28}ClN_3O_2 \cdot 0.2H_2O$: C, 69.65; H, 6.15; N, 9.03; found C, 69.60; H, 5.92; N, 8.95.

6-Chloro-5-(*N*,*N*-dimethylamino)-1-[4-[(2-methylbenzoyl)-amino]benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine (17). Using the same procedure as **14, 17** (70 mg, 9% from **12d**) was obtained from **13d** (0.3 g of crude material) as white powder: mp. 175–177°C; ^{1}H NMR ($CDCl_3$) δ 1.36–5.27 (7H, m), 2.21 (6H, s), 2.49 (3H, s), 6.60–7.76 (12H, m); MS (ES) m/z 461 $[M]^+$. Anal. calcd for $C_{27}H_{28}ClN_3O_2$: C, 70.20; H, 6.11; N, 9.10; found C, 69.74; H, 5.66; N, 9.12.

5-[(*N*-Allyl-*N*-methyl)amino]-7-Chloro-1-[4-[(2-methyl-benzoyl)amino]benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benz-azepine (19). Using the same procedure as **14, 19** (0.29 g, 57%) was obtained from **18** (0.49 g, 1 mmol) as white powder: mp. 181–184°C; ^{1}H NMR ($CDCl_3$) δ 1.23–2.67 (4H, m), 2.40 (3H, s), 2.44 (3H, s), 2.88–4.33 (5H, m), 5.07–5.37 (2H, m), 5.75–6.12 (1H, m), 7.07–7.73 (9H, m), 8.06 (1H, brs). Anal. calcd for $C_{29}H_{30}ClN_3O_2$: C, 71.37; H, 6.20; N, 8.61; found C, 71.30; H, 6.25; N, 8.51.

7-Chloro-5-hydroxy-1-[4-[(2-methylbenzoyl)amino]benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine (20). To a solution of **12a** (0.2 g, 0.46 mmol) in MeOH (30 mL), was added $NaBH_4$ (26 mg, 0.69 mmol) at room temperature. After stirred for 1 h, the mixture was concentrated. The resultant residue was diluted with $CHCl_3$, washed with H_2O, dried, concentrated, and recrystallized (MeOH–Et_2O) to give **20** (89 mg, 44%) as white powder: mp. 253–254; ^{1}H NMR ($CDCl_3$) δ 1.67–2.64 (4H, m), 2.45 (3H, s), 2.64–3.03 (2H, m), 4.68–5.16 (2H, m), 6.56 (1H, d, J = 8.0 Hz), 6.88–7.53 (9H, m), 7.58–7.82 (2H, m). Anal. calcd for $C_{25}H_{23}ClN_2O_3$: C, 69.04; H, 5.33; N, 6.44; found C, 68.90; H, 5.51; N, 6.24.

7-Chloro-5-hydroxy-1-(4-nitrobenzoyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (23). Using the same procedure as **20, 23** (8.94 g, 99%) was obtained from **10a** (9 g, 26 mmol) as yellow powder: ^{1}H NMR ($CDCl_3$) δ 1.53–2.94 (6H, m), 4.71–5.22 (2H, m), 6.52 (1H, d, J = 8.3 Hz), 6.95 (1H, dd, J = 8.3, 2.4 Hz), 7.21–7.40 (2H, m), 7.58–7.74 (1H, m), 7.92–8.12 (2H, m).

7-Chloro-5-methoxy-1-(4-nitrobenzoyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (24a). To a solution of **23** (1.5 g, 4.3 mmol) in DMF (15 mL) was added NaH (60% in oil, 0.19 g, 4.8 mmol) at 0–5°C. After H_2 ceased to be evolved, MeI (0.3 mL, 4.8 mmol) was added to the mixture. The mixture was stirred for 1 h at room temperature, poured into ice-water, and extracted with AcOEt. The organic layer was separated, washed with H_2O, dried ($MgSO_4$) and concentrated. The residue thus obtained was purified by silica gel column chromatography (eluent, *n*-hexane:AcOEt (1:1)) to provide **24a** (1.1 g, 71%) as yellow powder: ^{1}H NMR ($CDCl_3$) δ 1.47–3.06 (5H, m), 3.42–3.56 (total 3H, each s), 4.24–5.16 (2H, m), 6.54 (1H, d, J = 8.2 Hz), 6.88–7.02 (1H, m), 7.21–7.73 (3H, m), 7.96–8.18 (2H, m).

5-Allyloxy-7-chloro-1-(4-nitrobenzoyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (24b). Using the same procedure as **24a, 24b** (0.9 g, 81%) was obtained as yellow powder from **23** (9 g, 26 mmol) and allylbromide (0.27 mL, 3.1 mmol) instead of MeI: ^{1}H NMR ($CDCl_3$) δ 1.52–2.57 (4H, m), 2.67–3.03 (1H, m), 3.94–4.26 (2H, m), 4.40–5.48 (4H, m), 5.76–6.13 (1H, m), 6.53 (1H, d, J = 8.3 Hz), 6.83–7.03 (1H, m), 7.18–7.43 (2H, m), 7.50–7.67 (1H, m), 7.92–8.13 (2H, m); MS (ES) m/z 386 $[M]^+$.

1-(4-aminobenzoyl)-7-Chloro-5-methoxy-2,3,4,5-tetrahydro-1*H*-1-benzazepine (25a). Using the same procedure as **3a, 25a** (0.85 g, 93%) was obtained from **24a** (1 g, 2.8 mmol) as white powder: ^{1}H NMR ($CDCl_3$) δ 1.37–2.47 (4H,m), 2.62–3.03 (1H, m), 3.27–3.96 (5H, m), 4.14–4.87 (2H, m), 6.28–6.98 (2H, m), 6.52–6.70 (1H, m), 6.87–7.58 (4H, m).

5-Allyloxy-1-(4-aminobenzoyl)-7-chloro-2,3,4,5-tetrahydro-1*H*-1-benzazepine (25b). Using the same procedure as **3a**, **25b** (0.65 g, 78%) was obtained from **24b** (0.9 g, 2.3 mmol) as yellow powder: ^{1}H NMR ($CDCl_3$) δ 1.36–3.03 (5H, m), 3.68–4.85 (6H, m), 5.05–5.44 (2H, m), 5.77–6.13 (1H, m), 6.32–6.48 (2H, m), 6.52–6.72 (1H, m), 6.88–7.68 (4H, m).

7-Chloro-5-methoxy-1-[4-[(2-methylbenzoyl)amino]benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine (21). Using the same procedure as **12a, 21** (0.29 g, 72%) was obtained from **25a** (0.3 g, 0.91 mmol) as white powder: mp. 196.5–198.5°C; ^{1}H NMR ($CDCl_3$) δ 1.45–3.03 (5H, m), 2.48 (3H, s), 3.31–3.62 (3H, m), 4.22–5.18 (2H, m), 6.50–6.67 (1H, m), 6.88–7.05 (1H, m), 7.12–7.58 (10H, m); MS (ES) m/z 448 $[M]^+$. Anal. calcd for $C_{26}H_{25}ClN_2O_3$: C, 69.56; H, 5.61; N, 6.24; found C, 69.49; H, 5.44; N, 6.09.

5-Allyloxy-7-chloro-1-[4-[(2-methylbenzoyl)amino]benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine (22). Using the same procedure as **12a, 22** (0.19 g, 72%) was obtained from **25a** (0.2 g, 0.56 mmol) as white powder: mp. 129.5–131.5°C; ^{1}H NMR ($CDCl_3$) δ 1.48–3.04 (5H, m), 2.48 (3H, s), 3.97–4.86 (4H, m), 5.06–5.47 (2H, m), 5.83–6.13 (1H, m), 6.52–6.63 (1H, m), 6.90–7.04 (1H, m), 7.13–7.62 (10H, m); MS (ES) m/z 474 $[M]^+$. Anal. calcd for $C_{28}H_{27}ClN_2O_3$: C, 70.80; H, 5.73; N, 5.90; found C, 70.87; H, 5.53; N, 5.98.

7-Chloro-1-(2-chloro-4-nitrobenzoyl)-5-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine (27a). Using the same procedure as **10a, 27a** (16.6 g, 57%) was obtained as yellow powder from **9a** (15 g, 76.7 mmol) and **26a** (18.6 g, 84.5 mmol): mp. 125–126.5°C; ^{1}H NMR ($CDCl_3$) δ 1.87–2.45 (2H, m), 2.75–2.99 (2H, m), 3.13–5.33 (2H, m), 6.81–6.98 (1H, m), 7.07–7.44 (2H, m), 7.71 (1H, d, J= 2.5 Hz), 7.87–8.18 (2H, m); MS (ES) m/z 348 $[M–H]^+$.

7-Chloro-1-(3-chloro-4-nitrobenzoyl)-5-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine (27b). Using the same procedure as **10a, 27b** (7.25 g, 89%) was obtained as yellow powder from **9a** (4.2 g, 21.5 mmol) and **26b**[18] (4.5 g, 22.3 mmol): ^{1}H NMR ($CDCl_3$) δ 1.97–2.43 (2H, m), 2.78–2.97 (2H, m), 3.13–5.37 (2H, m), 6.51–6.76 (1H, m), 6.95–7.10 (1H, m), 7.22–7.35 (1H, m), 7.58 (1H, d, J = 1.7 Hz), 7.66 (1H, d, J = 8.3 Hz), 7.83 (1H, d, J = 2.5 Hz).

7-Chloro-1-(2-methyl-4-nitrobenzoyl)-5-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine (27c). Using the same procedure as **10a, 27c** (8.13 g, 32%) was obtained as white powder from **9a** (14 g, 71.6 mmol) and **26c**[19] (16.9 g, 93 mmol): ^{1}H NMR ($CDCl_3$) δ 1.75–2.66 (2H, m), 2.48 (3H, s), 2.72–3.04 (2H, m), 3.32–5.07 (2H, m), 6.66 (1H, d, J = 8.4 Hz), 6.95 (1H, d, J = 8.4 Hz), 7.08–8.35 (4H, m).

7-Chloro-1-(2-methoxy-4-nitrobenzoyl)-5-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine (27d). Using the same procedure as **10a, 27d** (11.6 g, 92%) was obtained as yellow powder from **9a** (6.6 g, 33.8 mmol) and **26d**[20] (10 g, 51 mmol). Pyridine (80 mL) was used as a solvent instead of Et_3N and CH_2Cl_2: ^{1}H NMR ($CDCl_3$) δ 1.69–2.48 (2H, m), 2.68–2.99 (2H, m), 3.03–5.20 (4H, m), 6.75 (1H, d, J = 8.4 Hz), 7.15 (1H, dd, J = 8.4, 2.6 Hz), 7.30–7.93 (4H, m).

7-Chloro-1-(3-methoxy-4-nitrobenzoyl)-5-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine (27e). Using the same procedure as **10a, 27e** (3.5 g, 31%) was obtained as yellow powder from **9a** (6 g, 30.7 mmol) and **26e**[21] (6.7 g, 34 mmol): ^{1}H NMR ($CDCl_3$) δ 1.91–2.37 (2H, m), 2.77–2.93 (2H, m), 3.17–5.07 (2H, m), 3.81 (3H, s), 6.62–6.87 (2H, m), 6.90–6.97 (1H, m), 7.26 (1H, dd, J = 8.3, 2.5 Hz), 7.65 (1H, d, J = 8.3 Hz), 7.77 (1H, d, J = 2.5 Hz).

1-(4-Amino-2-chlorobenzoyl)-7-chloro-5-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine (28a). Using the same procedure as **3a, 28a** (13.5 g, 95%) was obtained as yellow powder from **27a** (15.4 g, 40.6 mmol): mp. 188–191.5°C; ^{1}H NMR ($CDCl_3$) δ 1.78–2.33 (2H, m), 2.73–3.01 (2H, m), 3.34–4.67 (4H, m), 6.20–7.42 (5H, m), 7.64–7.87 (1H, m).

(4-Amino-3-chlorobenzoyl)-7-chloro-5-oxo-1-2,3,4,5-tetrahydro-1*H*-1-benzazepine (28b). Using the same procedure as **3a, 28b** (5.75 g, 86%) was obtained as yellow powder from **27b** (7.25 g, 19.1 mmol): ^{1}H NMR ($CDCl_3$) δ 2.01–2.27 (2H, m), 2.82–2.96 (2H, m), 3.65–4.67 (4H, m), 6.46 (1H, d, J = 8.4 Hz), 6.72 (1H, d, J = 8.5 Hz), 6.77 (1H, dd, J = 8.4, 2.0 Hz), 7.22 (1H, dd, J = 8.5, 2.5 Hz), 7.40 (1H, d, J = 2.0 Hz), 7.84 (1H, d, J = 2.5 Hz).

1-(4-Amino-2-methylbenzoyl)-7-chloro-5-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine (28c). Using the same procedure as **3a, 28c** (2.92 g, 39%) was obtained as white powder from **27c** (8.13 g, 22.7 mmol): mp. 190–191°C; ^{1}H NMR ($CDCl_3$) δ 1.22–2.43 (2H, m), 2.34 (3H, s), 2.73–3.00 (2H, m), 3.32–4.43 (4H, m), 6.12–6.30 (1H, m), 6.44 (1H, d, J = 2.1 Hz), 6.53–6.36 (2H, m), 7.20 (1H, dd, J = 8.5, 2.5 Hz), 7.77 (1H, d, J = 2.5 Hz). Anal. calcd for $C_{18}H_{17}ClN_2O_2$: C, 65.40; H, 5.24; N, 8.47; found C, 65.27; H, 5.03; N, 8.38.

1-(4-Amino-2-methoxybenzoyl)-7-chloro-5-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine (28d). Using the same procedure as **3a, 28d** (7.4 g, 89%) was obtained as white powder from **27d** (9 g, 24 mmol): ^{1}H NMR ($CDCl_3$) δ 1.82–2.33 (2H, m), 2.53–4.96 (6H, m), 3.36 (3H, s), 5.76–5.88 (1H, m), 6.23 (1H, dd, J = 8.2, 2.0 Hz), 6.62–6.83 (1H, m), 7.11 (1H, dd, J = 8.5, 2.5 Hz), 7.18–7.32 (1H, m), 7.79 (1H, d, J = 2.5 Hz).

1-(4-Amino-3-methoxybenzoyl)-7-chloro-5-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine (28e). Using the same procedure as **11a, 28e** (2.3 g, 83%) was obtained as yellow oil from **27e** (3 g, 8 mmol): ^{1}H NMR ($CDCl_3$) δ 2.03–2.24 (2H, m), 2.81–2.95 (2H, m), 3.57–4.38 (4H, m), 3.69 (3H, s), 6.41 (1H, d, J = 8.2 Hz), 6.64 (1H, dd, J = 8.2, 1.8 Hz), 6.71 (1H, d, J = 8.5 Hz), 6.80 (1H, d, J = 1.8 Hz), 7.19 (1H, dd, J = 8.5, 2.5 Hz), 7.81 (1H, d, J = 2.5 Hz).

7-Chloro-1-[2-chloro-4-[(2-methylbenzoyl)amino]benzoyl]-5-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine (29a). Using the same procedure as **12a, 29a** (7.8 g, 99%) was obtained as a colorless amorphous compound from **28a** (6 g, 17 mmol): ^{1}H NMR ($CDCl_3$) δ 1.76–2.31 (2H, m), 2.45 (3H, s), 2.56–5.17 (4H, m), 6.73–8.44 (11H, m); MS (ES) *m*/*z* 467 $[M-H]^+$.

7-Chloro-1-[3-chloro-4-[(2-methylbenzoyl)amino]benzoyl]-5-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine (29b). Using the same procedure as **12a, 29b** (3.78 g, 50%) was obtained as white powder from **28b** (5.7 g, 16.3 mmol): ^{1}H NMR ($CDCl_3$) δ 2.06–2.33 (2H, m), 2.53 (3H, s), 2.83–2.98 (2H, m), 3.16–4.98 (2H, m), 6.73 (1H, d, $J=8.5$ Hz), 7.07 (1H, dd, $J=8.6$, 2.0 Hz), 7.20–7.57 (6H, m), 7.87 (1H, d, $J=2.5$ Hz), 8.07 (1H, brs), 8.44 (1H, d, $J=8.6$ Hz).

7-Chloro-1-[2-methyl-4-[(2-methylbenzoyl)amino]benzoyl]-5-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine (29c). Using the same procedure as **12a, 29e** (1.67 g, 53%) was obtained as a colorless amorphous compound from **28c** (2.3 g, 7 mmol): ^{1}H NMR ($CDCl_3$) δ 1.93–2.25 (2H, m), 2.28–2.60 (2H, m), 2.36 (3H, s), 2.45 (3H, s), 2.73–2.97 (2H, m), 3.34–4.76 (2H, m), 6.43–8.05 (11H, m).

7-Chloro-1-[2-methoxy-4-[(2-methylbenzoyl)amino]benzoyl]-5-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine (29d). Using the same procedure as **12a, 29d** (10 g, quant.) was obtained as white powder from **28d** (7.4 g, 21.5 mmol): ^{1}H NMR ($CDCl_3$) δ 1.67–2.56 (2H, m), 2.48 (3H, s), 2.66–5.30 (7H, m), 6.75 (1H, d, $J=8.5$ Hz), 6.95 (1H, d, $J=8.3$ Hz), 7.06–7.50 (7H, m), 7.63 (1H, brs), 7.79 (1H, d, $J=2.5$ Hz).

7-Chloro-1-[3-methoxy-4-[(2-methylbenzoyl)amino]benzoyl]-5-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine (29e). Using the same procedure as **12a, 29c** (1 g, 61%) was obtained as yellow oil from **28e** (1.23 g, 3.6 mmol): ^{1}H NMR ($CDCl_3$) δ 1.98–2.33 (2H, m), 2.50 (3H, s), 2.75–2.96 (2H, m), 3.36–4.67 (2H, m), 3.73 (3H, s), 6.73 (1H, d, $J=8.5$ Hz), 6.82–6.96 (2H, m), 7.12–7.57 (5H, m), 7.82 (1H, d, $J=2.5$ Hz), 8.14 (1H, brs), 8.38 (1H, d, $J=8.3$ Hz).

7-Chloro-1-[2-choloro-4-[(2-methylbenzoyl)amino]benzoyl]-5-hydroxy-2,3,4,5-tetrahydro-1*H*-1-benzazepine (30). Using the same procedure as **20, 30** (0.12 g, 40%) was obtained as a colorless amorphous compound from **29a** (0.3 g, 0.64 mmol): ^{1}H NMR ($CDCl_3$) δ 1.42–3.85 (6H, m), 2.36 (3H, s), 4.33–5.18 (2H, m), 6.68–8.02 (10H, m), 8.27–8.60 (1H, m). Anal. calcd for $C_{25}H_{22}Cl_2N_2O_3 \cdot 0.5H_2O$: C, 62.77; H, 4.85; N, 5.86; found C, 62.63; H, 5.00; N, 5.49.

7-Chloro-1-[3-choloro-4-[(2-methylbenzoyl)amino]benzoyl]-5-hydroxy-2,3,4,5-tetrahydro-1*H*-1-benzazepine (31). Using the same procedure as **20, 31** (1.2 g, 98%) was obtained as colorless needles from **29b** (1.2 g, 2.6 mmol): mp. 256–258°C; ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ 1.55–2.95 (5H, m), 2.51 (3H, s), 4.68–5.15 (2H, m), 6.53–6.71 (1H, m), 6.90–7.83 (8H, m), 8.07–8.42 (2H, m). Anal. calcd for $C_{25}H_{22}Cl_2N_2O_3$: C, 63.97; H, 4.72; N, 5.97; found C, 63.87; H, 4.44; N, 5.86.

7-Chloro-5-hydroxy-1-[2-methyl-4-[(2-methylbenzoyl)-amino]benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine (32). (OPC-41061) Using the same procedure as **20, 32** (93 mg, 30%) was obtained as colorless prisms from **29c** (0.31 g, 0.69 mmol): mp. 225.9°C; ^{1}H NMR (DMSO-d_6) δ 1.35–3.23 (4H, m), 2.34 (6H, s), 4.46–5.04 (2H, m), 5.55–5.80 (1H, m), 6.53–7.84 (10H, m), 10.12–10.47 (1H, m); MS (ES) *m*/*z* 448 $[M]+$. Anal. calcd for $C_{26}H_{25}Cl_2N_2O_3$: C, 69.56; H, 5.61; N, 6.24; found C, 69.40; H, 5.51; N, 6.35.

7-Chloro-5-hydroxy-1-[2-methoxy-4-[(2-methylbenzoyl)-amino]benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine (33). Using the same procedure as **20, 33** (6.8 g, 75%) was obtained as a colorless amorphous compound from **29d** (9 g, 19.5 mmol): ^{1}H NMR ($CDCl_3$) δ 1.33–2.52 (4H, m), 2.42 (3H, s), 2.56–2.82 (1H, m), 2.93–3.95 (1H, m), 3.46 (3H, s), 4.47–5.12 (2H, m), 6.55–7.73 (10H, m), 8.23 (1H, brs). Anal. calcd for $C_{26}H_{25}ClN_2O_4 \cdot 0.2H_2O$: C, 66.65; H, 5.46; N, 5.98; found C, 66.48; H, 5.22; N, 5.81.

7-Chloro-5-hydroxy-1-[3-methoxy-4-[(2-methylbenzoyl)-amino]benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine (34). Using the same procedure as **20, 34** (3.66 g, 80%) was obtained as colorless prisms from **29e** (4.58 g, 9.9 mmol): ^{1}H NMR ($CDCl_3$) δ 1.37–2.25 (4H, m), 2.39 (3H, s), 2.57–2.84 (1H, m), 3.53–3.28 (3H, m), 4.56–5.08 (2H, m), 5.57–5.86 (1H, m), 6.64–7.65 (9H, m), 7.69–7.90 (1H, m), 9.18–9.33 (1H, m). Anal. calcd for $C_{26}H_{25}ClN_2O_4$: C, 67.16; H, 5.42; N, 6.03; found C, 67.07; H, 5.30; N, 6.04.

AVP receptor binding assay

The procedures for radio-ligand binding assays were reported in detail.[5,23] IC_{50} values are the concentrations of compounds which inhibit [^{3}H]-AVP binding by 50%. All assays were performed in duplicate. The intraassay and interassay IC_{50} values for the given compounds may vary by less than 3% and less than 20%, respectively.

In vivo experiments

Male Sprague–Dawley rats (body weight: 280–340 g, Charles River Japan, Tokyo) at 8 weeks of age were orally given the test compounds in consecutive three or four doses selected among 0.3, 1, 3, 10, or 30 mg/kg, or vehicle (1% hydroxypropyl ethyl cellulose, polyethylene glycol or 5% gum arabic) ($n=3$ to 7 per each group). The rats were individually placed in metabolic cages and spontaneously voided urine was collected over a period of 0–2 h. During the study, drinking water and food were given ad libitum. To estimate the diuretic efficacy, the dose (ED_3; mg/kg) required to triple the urine volume compared to the control was calculated from at least three doses. The mean value for the urine volume accumulated for 2 h in the control rats was 1.1 ± 0.2 mL ($n=4$). The care and handling of the animals were in accordance with The Guidelines for Animal Experimentations in Otsuka Pharmaceutical Co., Ltd., 1 October 1994.

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