Nonpeptide Arginine Vasopressin Antagonists for Both V_{1A} and V_2 Receptors: Synthesis and Pharmacological Properties of 4′-[5-(Substituted Methylidene)-2,3,4,5-tetrahydro-1*H*-1-benzoazepine-1-carbonyl]benzanilide and 4′-[5-(Substituted Methyl)-2,3-dihydro-1*H*-1-benzoazepine-1-carbonyl]benzanilide Derivatives

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Arginine vasopressin (AVP) has a dual action, *i.e.* vasoconstriction and water reabsorption *via* V_{1A} and V_2 receptors, and may play a role in a number of diseases, including congestive heart failure (CHF), hypertension, renal disease, edema, and hyponatremia. We have attempted to develop a new series of AVP antagonists for both V_{1A} and V_2 receptors based on the hypothesis that the blockade of both V_{1A} and V_2 receptors might be beneficial to CHF patients. In this report, a series of compounds structurally related to 4′-[5-(substituted methylidene)-2,3,4,5-tetrahydro-1*H*-1-benzoazepine-1-carbonyl]benzanilide (*exo*-olefin isomer) and 4′-[5-(substituted methyl)-2,3-dihydro-1*H*-1-benzoazepine-1-carbonyl]benzanilide (*endo*-olefin isomer) were synthesized and examined to have AVP antagonist activity for both V_{1A} and V_2 receptors. As a result, it was found that the (*E*)-*exo*-olefin isomers showed more potent binding affinitiy compared with *endo*-olefin isomers. Among these (*E*)-*exo*-olefin isomers, (*E*)-*N*-methyl-{1-[4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzoazepin-5-ylidene}acetamide (14) exhibited the most potent binding affinitiy and (*E*)-*N*-methyl-(1-{4-[2-(4-methylphenyl)benzoylamino]benzoyl}-2,3,4,5-tetrahydro-1*H*-1-benzoazepin-5-ylidene)acetamide (20) exhibited a high AVP antagonist activity for both V_{1A} and V_2 receptors after intravenous administration. Details of the synthesis and pharmacological properties of this series are presented.

Key words arginine vasopressin antagonist; benzoazepine; congestive heart failure; benzanilide; antidiuretic hormone

Arginine vasopressin (AVP) is a peptide hormone which is released from the posterior pituitary and exerts a variety of biological effects. Two subtypes of the AVP receptor have been identified as V_{1A} and V_2 in the periphery.[1] The V_{1A} receptor activates inositol-1,4,5-trisphosphate turnover and is responsible for the effects of AVP on the cardiovascular system, such as the vasoconstriction of arterial smooth muscles.[1] The V_2 receptor mediates adenylate cyclase activation and plays a major role in the kidney, associated with the antidiuretic response to AVP which promotes water reabsorption.[2] AVP has a dual action, *i.e.* vasoconstriction and water reabsorption *via* V_{1A} and V_2 receptors, and may play a role in a number of diseases, including congestive heart failure (CHF), hypertension, renal disease, edema, and hyponatremia.[3]

Many reports have indicated that AVP plays a role in CHF, and that patients with CHF have high plasma levels of AVP.[4,5] Furthermore, most CHF patients with hyponatremia exhibited inappropriate secretion of AVP, which results in a highly unfavorable long-term prognosis.[6,7] Therefore, an AVP receptor antagonist could be a useful tool for treating CHF. Recently, it was reported that the peptide analogue, d$(CH_2)_5$-D-Tyr(Et)VAVP, which is an antagonist of both V_{1A} and V_2 receptors, produced significant hemodynamic improvements and water diuresis, without much change in systemic blood pressure in rats with markedly impaired left ventricular function.[8] Furthermore, combined administration of the V_{1A}-selective antagonist OPC-21268 (Fig. 1) and the V_2-selective antagonist OPC-31260 (Fig. 1) could induce not only metabolic and hormonal responses but also more beneficial hemodynamic responses, such as a prolonged reduction in mean arterial pressure and a profound increase in cardiac output in conscious dogs compared with treatment with a V_{1A}-selective antagonist alone.[9] These reports suggested that the blockade of both V_{1A} and V_2 receptors might be beneficial to CHF patients.

Based on this hypothesis, we have attempted to develop new AVP antagonists for both V_{1A} and V_2 receptors. Since AVP showed similar binding affinity for both V_{1A} and V_2 receptors,[10] we decided to search for a compound which would also have similar binding affinity for both V_{1A} and V_2 receptors. In a previous paper,[11] we described a series of 2-phenyl-4′-(2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-carbonyl)benzanilide derivatives. In the case of these benzodiazepine derivatives, introduction of a 5-substituent group, such as pyridylmethyl, carbamoylmethyl, and aminoalkyl, to the 5-position of the benzodiazepine moiety produced potent binding affinity and antagonist activity for both V_{1A} and V_2 receptors (**1**, Fig. 2). On the basis of these results, we then attempted to replace the 5-substituted benzodiazepine with a 5-substituted benzoazepine. OPC-31260 derivatives have been previously reported as 5-substituted benzoazepines.[12] These compounds have a C–N or C–O bond on the 5-position of benzoazepine and showed V_2-selective antagonist activity

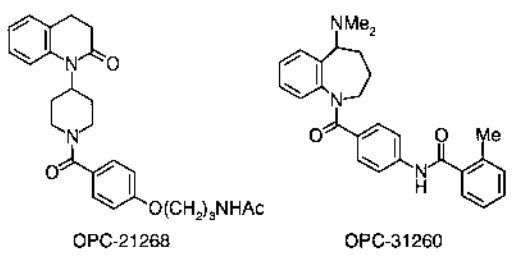

Fig. 1

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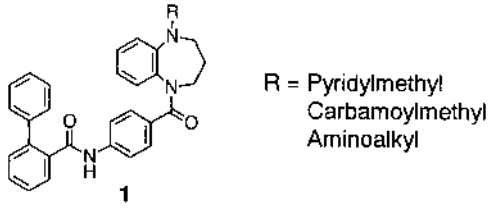


Fig. 2. 5-Substituted Benzodiazepine Derivatives

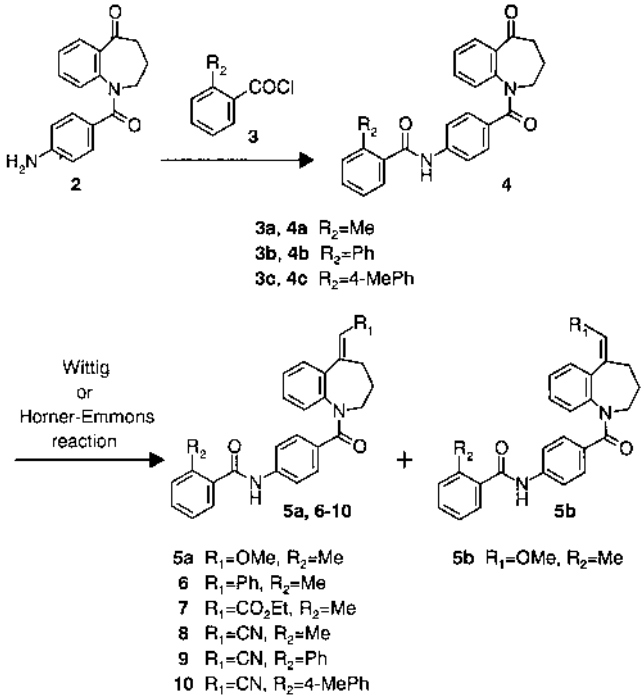


Chart 1

which was not our aim. Therefore, we attempted to introduce a 5-substituent group like those of our benzodiazepine derivatives to enhance the binding affinity and antagonist activity for both V_{1A} and V_2 receptors. In addition, since the presence of a chiral center seemed to be a disadvantage as far as synthesis was concerned, the introduction of a C=C bond at the 5-position of the benzoazepine ring was investigated.

In this report, the 5-(substituted methylidene)-2,3,4,5-tetrahydro-1*H*-1-benzoazepine derivatives (*exo*-olefin isomer) and 5-(substituted methyl)-2,3-dihydro-1*H*-1-benzoazepine derivatives (*endo*-olefin isomer) were investigated. We describe here the synthesis and biological activity of these compounds.

Chemistry

The synthetic pathways for the preparation of the *exo*-olefin and *endo*-olefin derivatives listed in Tables 1—4 are shown in Charts 1—3.

The *exo*-olefin derivatives were generally synthesized according to the route shown in Chart 1. The key intermediate benzoazepin-5-one derivatives (**4**) were obtained by condensation of 1-(4-aminobenzoyl)-2,3,4,5-tetrahydro-1*H*-1-benzoazepin-5-one (**2**)[12] with benzoyl chloride derivatives (**3**). We attempted the C=C bond formation using the Wittig or Horner–Emmons reaction. Condensation of **4a**[12] and (methoxymethyl)triphenylphosphonium chloride gave two methoxy-

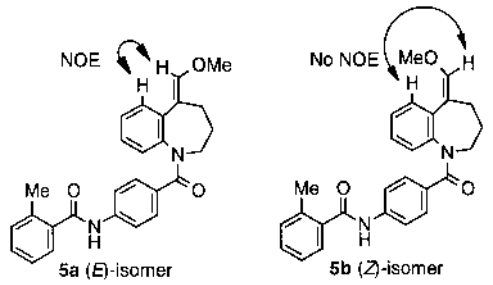


Fig. 3. Determination of the Configurations for **5a** and **5b** Using NOE Experiments

substituted *exo*-olefin isomers (**5a** and **5b**). These two isomeric forms could be distinguished by nuclear Overhauser effect (NOE) analysis (Fig. 3). **5a** showed an NOE effect between the methylidene proton and the proton at the C-6 position of benzoazepine, whereas **5b** did not show this NOE effect. As the result, **5a** was identified as the (*E*)-isomer and **5b** the (*Z*)-isomer. The phenyl-substituted *exo*-olefin derivative (**6**) was obtained under reflux conditions in tetrahydrofuran (THF), however, the 4-substituted phenyl derivatives (CN, NH_2, and OEt) and pyridyl derivatives could not be obtained under similar conditions. Ethoxycarbonyl (**7**) and cyano (**8**) substituted *exo*-olefin derivatives were obtained by condensation of **4a** and each Horner–Emmons reagent. In the case of phenyl (**4b**) and 4-methylphenyl (**4c**) as R_2, the cyano-substituted *exo*-olefin derivatives (**9** and **10**) were obtained under similar conditions to **8**, however, methoxy, phenyl, and ethoxycarbonyl substituted *exo*-olefin derivatives could not be obtained under similar conditions to these used for the synthesis of **5**—**7**. From these results, the reactivity of the 5-oxo group of benzoazepine seemed to be affected by the R_2 group. Compounds **6**—**10** were distinguished as (*E*)-isomers by NOE analysis. Since these (*E*)-isomers were produced as the major compound and isolation of both isomers was difficult, pure (*Z*)-isomers could not be obtained except in the case of methoxy-substituted derivative (**5b**).

Other *exo*-olefin and *endo*-olefin derivatives were synthesized according to the routes shown in Charts 2 and 3. We attempted the hydrolysis of **7** to obtain the carboxyl-substituted *exo*-olefin derivative (**11**). When **7** was treated with 1 N NaOH, a 1 : 1 mixture of two carboxylic acid isomers was obtained, so that individual isomers could not be isolated. Likewise, the hydrolysis of **7** with concentrated HCl and acetic acid produced a 7:1 mixture. In this case, only the major compound (**11**) could be isolated by recrystallization. **11** was identified as the (*E*)-*exo*-olefin isomer by ^{1}H-NMR and NOE analysis. Similar isomerization occurred following treatment of **7** with K_2CO_3 to give a 1 : 2 mixture of **7** and another isomer (**12**). **12** was isolated by chromatography and the structure was identified as the *endo*-olefin isomer by ^{1}H-NMR analysis, which showed methylene protons (δ 3.52 and δ3.93, each d, J=16 Hz) and olefin proton at the C-4 position of benzoazepine (δ 6.26, t, J=6.0 Hz). This was supported by observing NOE effects between each methylene proton and the protons at the C-4 and C-6 positions of benzoazepine (Fig. 4). The carboxyl-substituted *endo*-olefin derivative (**13**) was obtained by hydrolysis of **12** with concentrated HCl and acetic acid. By comparing the analysis data, the isomer produced by hydrolysis of **7** was found to be the *endo*-olefin iso-

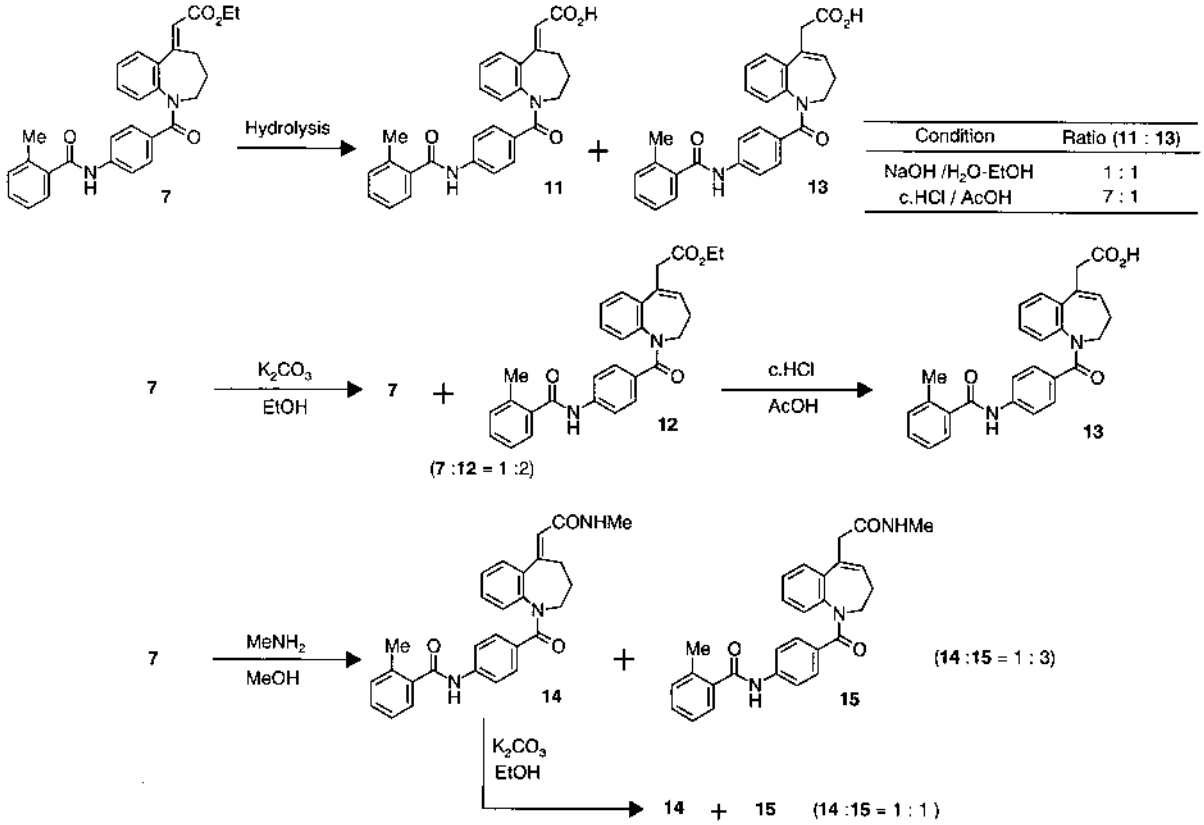


Chart 2

mer (**13**). Furthermore, the ester–amide exchange of **7** with methylamine caused a similar isomerization to give *N*-methylcarbamoyl-substituted *exo*-olefin (**14**) and *endo*-olefin (**15**) isomers in the ratio 1 : 3. This isomerization occurred following treatment of **14** with K_2CO_3 (**14** : **15**=1 : 1) as with **7**. It was found that the *exo*-olefin isomer was susceptible to isomerization to the *endo*-olefin isomer under both acidic and basic conditions. Similar *exo–endo* isomerization might have occurred during C=C bond formation by the Wittig or Horner–Emmons reaction. However, produce of *endo*-olefin isomer was not confirmed in the case of synthesis of **5**—**10**.

Carbamoyl-substituted derivatives, which have phenyl and 4-methylphenyl as R_2, were synthesized according to the routes shown in Chart 3. Since the target compounds could not be obtained from **4** as described above, we attempted the Horner–Emmons reaction of **2** with triethyl phosphonoacetate to give a mixture of key intermediate ethoxycarbonyl-substituted *exo*-olefin and *endo*-olefin isomers (**16**). The ester–amide exchange of **16** with methylamine, followed by recrystallization and chromatographic purification, gave the *N*-methylcarbamoyl-substituted *exo*-olefin (**17**) and *endo*-olefin (**18**) isomers. The desired benzanilide derivatives (**19**—**22**) were obtained by the condensation of **17** or **18** with 2-phenylbenzoyl chloride derivatives (**3b** and **3c**). On the other hand, the condensation of **16** with 2-phenylbenzoyl chloride (**3b**), followed by ester hydrolysis, gave a mixture of carboxyl-substituted *exo*-olefin and *endo*-olefin isomers (**24**), which were converted to *N*-(2-pyridylmethyl)carbamoyl-substituted derivatives. The *exo*-olefin (**25**) and *endo*-olefin (**26**) isomers were isolated by chromatography. (4-Methylpiperazin-1-yl)carbonyl-substituted derivatives (**27** and **28**) were obtained in the same manner. These carbamoyl-substituted *exo*-olefin derivatives (**14**, **17**, **19**, **20**, **25**, and **27**) were identified as the (*E*)-isomer by ^{1}H-NMR and NOE analysis.

5-(*N*-Methylcarbamoyl)methyl-substituted benzoazepine and 1,5-benzodiazepine derivatives were synthesized to compare the binding affinity potentials (Chart 4). The olefin moiety of **7** was reduced by catalytic hydrogenation, followed by ester–amide exchange, to give the (*N*-methylcarbamoyl)-methyl-substituted derivative (**30**). Condensation of ethyl [5-(4-aminobenzoyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-1-yl]acetate (**31**)[11] and **3a** gave the benzanilide derivative (**32**). The desired (*N*-methylcarbamoyl)methyl-substituted derivative (**33**) was obtained by ester–amide exchange of **32** with methylamine.

Results and Discussion

Binding Affinity The methods for determining the *in vitro* AVP receptor-binding affinity (rat liver for V_{1A} and rabbit kidney for V_2[13]) are described in a previous paper.[11] The results of the binding assay of compounds (**5**—**15**, **19**—**22**, **25**—**28**, **30**, and **33**) are shown in Tables 1—3.

As the initial modification, to examine the effect of the introduction of the *exo*-olefin moiety at the 5-position of the benzoazepine ring, methoxy (**5**), phenyl (**6**), ethoxycarbonyl (**7**), and cyano (**8**—**10**) substituted *exo*-olefin derivatives were prepared and tested (Table 1). In the case of the methoxy-substituted derivatives, the (*E*)-isomer (**5a**) exhibited 15-fold more potent V_{1A} receptor binding affinity compared with the (*Z*)-isomer (**5b**). It seemed that the binding affinity potential might be affected by the orientation of the 5-substituent group. The phenyl-substituted derivative (**6**)

maintained the binding affinity potential, whereas the ethoxycarbonyl (**7**) and cyano (**8**) substituted derivatives had lower V_{1A} receptor binding affinity compared with **5a**. Therefore, we attempted to synthesize pyridyl-substituted derivatives which were expected to show potent binding affinity, unfortunately, these compounds could not be obtained. Among the cyano-substituted derivatives (**8**—**10**), the 2-phenylbenzanilide derivative (**9**, R_2=Ph) exhibited the most potent binding affinity, in particular, its V_2 receptor binding affinity was the most potent of any compound in our investigations. However, **9** exhibited a 76-fold selectivity toward V_2 *versus* the V_{1A} receptor, which was unsatisfactory as far as our objective was concerned.

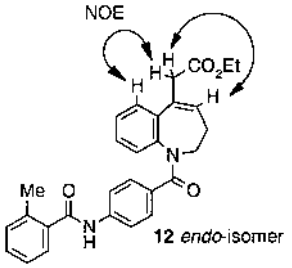


Fig. 4. Determination of the Configurations for **12** Using NOE Experiments

As the next modification, we investigated introduction of the carbamoyl-substituent group into the *exo*-olefin derivative, since this was effective in increasing the binding affinity potential in the case of the 1,5-benzodiazepine derivatives.[11] In the synthesis of these compounds, not only the *exo*-olefin isomers but also the *endo*-olefin isomers were obtained and tested (Table 2). A comparison of the results of the ethoxycarbonyl (**7** and **12**), carboxyl (**11** and **13**), and carbamoyl (**14**, **15**, **19**—**22**, and **25**—**28**) substituted derivatives suggested that introduction of the carbamoyl group was also effective in increasing the binding affinity potential. Among the carbamoyl-substituted *exo*-olefin isomers, the binding affinity potential increased in the order: *N*-(2-pyridylmethyl)-carbamoyl (**25**)>(4-methylpiperazin-1-yl)carbonyl (**27**)>*N*-methylcarbamoyl (**19**). The order for the *endo*-olefin isomers (**21**, **26**, and **28**) was the same as for the *exo*-olefin isomers.

In the case of carbamoyl-substituted derivatives, the *exo*-olefin isomers (**14**, **19**, **20**, **25**, and **27**) exhibited more potent binding affinity than the corresponding *endo*-olefin isomers (**15**, **21**, **22**, **26**, and **28**), except for the V_2 binding affinity of **19** *versus* **21**. In particular, the *N*-methylcarbamoyl-substi-

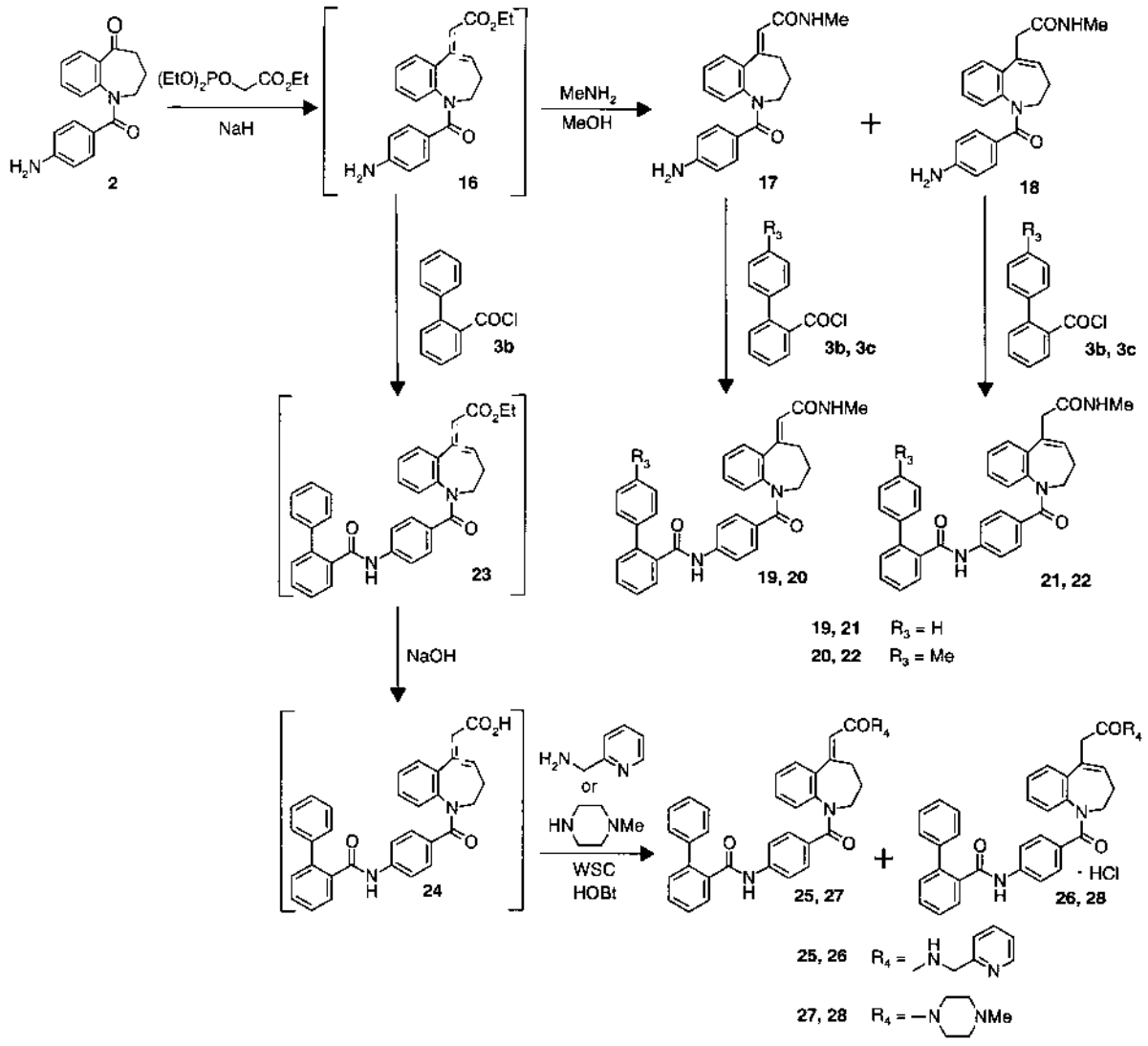


Chart 3

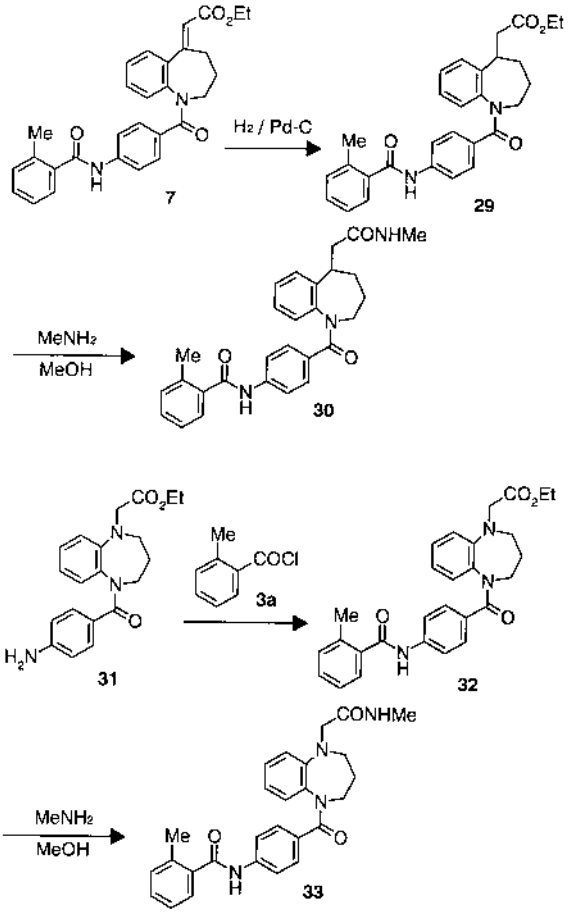
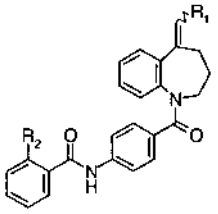


Chart 4

Table 1. Receptor-Binding Affinities for *Exo*-Olefin Derivatives

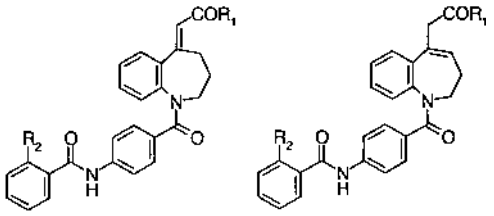


No.	R_1	R_2	Binding affinity (pK_i)	
			V_{1A} [a]	V_2 [b]
5a	(*E*)-OMe	Me	7.82	8.15
5b	(*Z*)-OMe	Me	6.65	8.01
6	(*E*)-Ph	Me	7.78	7.79
7	(*E*)-CO_2Et	Me	6.80	7.56
8	(*E*)-CN	Me	7.13	7.87
9	(*E*)-CN	Ph	8.52	10.4
10	(*E*)-CN	4-MePh	7.64	7.41

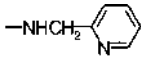
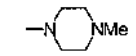
a) pK_i of [^{3}H]vasopressin binding to rat liver membranes. *b*) pK_i of [^{3}H]vasopressin binding to rabbit kidney membranes.

tuted *exo*-olefin isomer (**14**) showed a 2200-fold increase in V_{1A} receptor affinity compared with the *endo*-olefin isomer (**15**). From these results, fixing the orientation of the substituent group by means of the *exo*-olefin moiety seemed to increase the binding affinity potential. Furthermore, it seemed that this effect was more important for the V_{1A} receptor compared with the V_2 receptor.

Table 2. Receptor-Binding Affinities for (*E*)-*Exo*- and *Endo*-Olefin Isomers

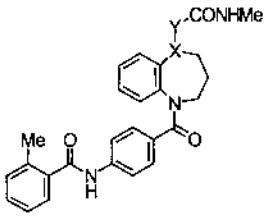


(*E*)-*Exo*-olefin isomers *Endo*-olefin isomers

R_1	R_2	Binding affinity (pK_i)					
		(*E*)-*Exo*-olefin isomers			*Endo*-olefin isomers		
		No.	V_{1A} [a]	V_2 [b]	No.	V_{1A} [a]	V_2 [b]
OEt	Me	**7**	6.80	7.56	**12**	6.30	7.14
OH	Me	**11**	6.04	7.32	**13**	5.66	7.76
NHMe	Me	**14**	9.89	10.32	**15**	6.55	9.09
NHMe	Ph	**19**	8.86	8.29	**21**	7.76	8.40
NHMe	4-MePh	**20**	8.71	9.25	**22**	8.10	9.01
	Ph	**25**	9.16	9.40	**26**	7.99	8.81
	Ph	**27**	8.88	9.04	**28**	7.93	8.54

a, *b*) See footnotes in Table 1.

Table 3. Receptor-Binding Affinities for Benzoazepine and Benzodiazepine Derivatives



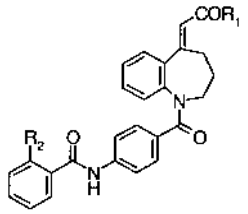
No.		Binding affinity (pK_i)	
		V_{1A} [a]	V_2 [b]
14		9.89	10.3
30		7.44	8.69
33		6.58	8.67

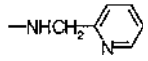
a, *b*) See footnotes in Table 1.

Among the *N*-methylcarbamoyl-substituted *exo*-olefin isomers (**14**, **19**, and **20**), the 2-methylbenzanilide derivative (**14**, R_2=Me) exhibited the most potent binding affinity for both V_{1A} and V_2 receptors. However, among the *endo*-olefin isomers (**15**, **21**, and **22**), the 2-(4-methylphenyl)benzanilide derivative (**22**, R_2=4-MePh) exhibited the most potent binding affinity. As described above, the 2-phenylbenzanilide derivative (**9**) exhibited the most potent binding affinity among the cyano-substituted derivatives (**8**—**10**). No relationship between the R_2 group and binding affinity could be found.

The (*N*-methylcarbamoyl)methyl-substituted benzoazepine (**30**) and 1,5-benzodiazepine (**33**) derivatives were prepared and compared with the *exo*-olefin derivative (**14**) (Table 3).

Table 4. AVP-Antagonist Activities for (*E*)-*Exo*-Olefin Derivatives



No.	R_1	R_2	Binding affinity (pK_i)		Antagonist activity	
			V_{1A}	V_2	V_{1A} ID_{50} (mg/kg)[a]	V_2 ED_3 (mg/kg)[b]
14	NHMe	Me	9.89	10.3	0.040	1.97
20	NHMe	4-MePh	8.71	9.25	0.022	0.039
25		Ph	9.16	9.40	0.0092	0.18

a) ID_{50} represents the drug concentration (mg/kg) required to inhibit the AVP-induced pressor response in pithed rats by 50% following intravenous administration. *b*) ED_3 represents the drug concentration (mg/kg) required to increase urine volume by 3 ml during 2 h after intravenous administration of the drug to rats.

30 and **33** exhibited lower binding affinity potentials for both V_{1A} and V_2 receptors than **14**.

As a consequence, it was suggested that fixing the orientation of the substituent group to the *entgegen* site by the *exo*-olefin moiety on the 5-position of benzoazepine was effective in increasing the binding affinity potential from the results described below. (1) The methoxy-substituted (*E*)-*exo*-olefin isomer (**5a**) was more potent than the corresponding (*Z*)-isomer (**5b**). (2) The carbamoyl-substituted *exo*-olefin isomers were more potent than the corresponding *endo*-olefin isomers. (3) The *N*-methylcarbamoyl-substituted *exo*-olefin derivative (**14**) was more potent than the (*N*-methylcarbamoyl)methyl-substituted benzoazepine (**30**) and benzodiazepine (**33**) derivatives.

Antagonist Activity The V_{1A} receptor antagonist activity was determined by measuring inhibition of the AVP-induced diastolic blood pressure (DBP) response in pithed rats after intravenous (i.v.) administration. We determined the dose of the compounds causing a 50% inhibition of the pressor response to AVP (ID_{50}). The V_2 receptor antagonist activity was determined by measuring the effect on urine volume in dehydrated conscious rats after i.v. administration. We determined the dose causing an increase in urine volume by 3 ml during 2 h after administering the compound (ED_3). The experimental method for determining AVP antagonist activity was described in a previous paper.[11)]

Compounds **14**, **20**, and **25**, which showed potent binding affinity for both V_{1A} and V_2 receptors, were selected and tested *in vivo* (Table 4). Among these compounds, **20** and **25** exhibited potent antagonist activity for both V_{1A} and V_2 receptors. Furthermore, **20** produced an increase in urine volume (10.7 ± 0.63 ml in 2 h) after oral administration (10 mg/kg) to dehydrated conscious rats.[14)] However, **14** showed less antagonist activity compared with **20** and **25** in contrast to these high binding affinity potentials. The reason for this dissociation of *in vitro* binding affinity and *in vivo* antagonist activity potential was unclear since further pharmacological investigation such as determining the partial agonist activity and pharmacokinetics of these compounds were not performed.

Conclusions

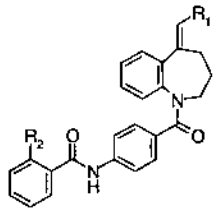
In this report, 5-(substituted methylidene)-2,3,4,5-tetrahydro-1*H*-1-benzoazepine and 5-(substituted methyl)-2,3-dihydro-1*H*-1-benzoazepine derivatives, *i.e.* compounds which have a C=C bond at the 5-position of the benzoazepine, were synthesized as a new series of AVP antagonists of both V_{1A} and V_2 receptors, and their pharmacological properties were evaluated. It was found that the introduction of a (*E*)-carbamoylmethylidene group at the 5-position of the benzoazepine enhanced the binding affinity potential for both V_{1A} and V_2 receptors and the (*E*)-*exo*-olefin isomers exhibited more potent binding affinity compared with the *endo*-olefin isomers. In particular, (*E*)-*N*-methyl-{1-[4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzoazepin-5-ylidene}acetamide (**14**) exhibited potent binding affinity and (*E*)-*N*-methyl-(1-{4-[2-(4-methylphenyl)benzoylamino]benzoyl}-2,3,4,5-tetrahydro-1*H*-1-benzoazepin-5-ylidene)acetamide (**20**) exhibited high antagonist activity following i.v. administration. We hope that a dual V_{1A} and V_2 receptor antagonist, like **20**, will be useful for the treatment of cardiovascular diseases such as CHF.

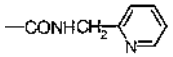
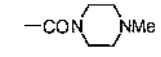
Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus without correction. ^{1}H-NMR spectra were recorded on JNM-LA400, LA500, and A500 spectrometers using tetramethylsilane as an internal standard. MS spectra were determined on a Hitachi M-80 or JEOL JMS-DX300 spectrometer. Elemental analysis data were within ±0.4% of the calculated values, unless otherwise noted. HPLC analyses were performed on a TOSOH TSK-GEL ODS-80TM column (4.6×150 mm). All organic extracts were dried over anhydrous $MgSO_4$. Chromatographic purification were performed on Merck KGaA Silica gel 60 (0.040—0.063 mm).

2-Methyl-4′-(5-oxo-2,3,4,5-tetrahydro-1*H*-1-benzoazepine-1-carbonyl)benzanilide (4a)[12)] To an ice-cooled solution of 1-(4-aminobenzoyl)-2,3,4,5-tetrahydro-1*H*-1-benzoazepin-5-one (**2**)[12)] (9.7 g) and Et_3N (3.5 g) in CH_2Cl_2 (100 ml) were added a solution of 2-methylbenzoyl chloride (**3a**) (5.35 g) in CH_2Cl_2 (15 ml), and the mixture was stirred for 2 h at room temperature. The mixture was washed with water and brine, dried, and then concentrated. The residue was collected by filtration and washed with diethylether (Et_2O) to give **4a** (13.8 g, quantitative yield) as a colorless powder, mp 239—242 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.0—2.3 (2H, m, azepine), 2.47 (3H, s, Me), 2.8—3.0 (2H, m, azepine), 3.4—3.6 (1H, m, azepine), 4.4—4.6 (1H, m, azepine), 6.76 (1H, d, J=8.0 Hz, H-9 of benzoazepine), 7.1—7.9 (11H, m, Ar-H). FAB-MS *m/z*: 399 (M^++1). *Anal.* Calcd for $C_{25}H_{22}N_2O_3 \cdot 2/3H_2O$: C, 73.15; H, 5.73; N, 6.82. Found: C, 72.76; H, 5.47; N, 6.76.

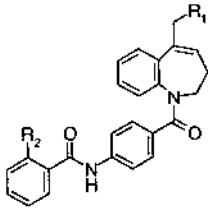
Table 5. Physical and Spectral Data of (*E*)-*Exo*-Olefin Derivatives

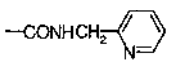
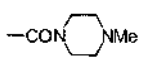


No.	R_1	R_2	Yield (%)[a]	mp (°C)	Formula[b]	^{1}H-NMR ($CDCl_3$) δ	MS *m/z* (M^++1)
5a	OMe	Me	43	201—204	$C_{27}H_{26}N_2O_3 \cdot 1/2H_2O$	1.7—1.8 (1H, m, azepine), 1.9—2.0 (1H, m, azepine), 2.3—2.4 (1H, m, azepine), 2.47 (3H, s, MePh), 2.8—2.9(1H, m, azepine), 3.0—3.1 (1H, m, azepine), 3.77 (3H, s, MeO), 4.7—4.8 (1H, m, azepine), 6.25 (1H, s, C=CHOMe), 6.65 (1H, d, *J*=8.0 Hz, H-9 of benzoazepine), 6.95 (1H, t, *J*=7.5 Hz, H-8 of benzoazepine), 7.1—7.5 (10H, m, Ar-H)	427
6	Ph	Me	38	120—124	$C_{32}H_{28}N_2O_2$	1.8—2.2 (2H, m, azepine), 2.46 (3H, s, Me), 2.5—2.7 (1H, m, azepine), 3.0—3.3 (2H, m, azepine), 4.7—4.9 (1H, m, azepine), 6.71 (1H, s, C=CHPh), 7.0—7.5 (17H, m, Ar-H)	473
7	CO_2Et	Me	3.2	143—145	$C_{29}H_{28}N_2O_4 \cdot 1/3H_2O$	1.34 (3H, t, *J*=7.3 Hz, CH_2CH_3), 1.7—2.2(2H, m, azepine), 2.44 (3H, s, Me), 2.9—3.5 (3H, m, azepine), 4.24 (2H, q, *J*=6.7 Hz, CH_2CH_3), 4.4—4.6 (1H, m, azepine), 6.04 (1H, s, C=CHCO), 6.67 (1H, d, *J*=6.1 Hz, H-9 of benzoazepine), 7.0—7.5 (11H, m, Ar-H)	469
8	CN	Me	59	220—224	$C_{27}H_{23}N_3O_2$	1.9—2.2 (2H, m, azepine), 2.46 (1H, s, Me), 2.5—2.7 (1H, m, azepine), 2.8—3.0 (2H, m, azepine), 4.6—4.8 (1H, m, azepine), 5.57 (1H, s, C=CHCN), 6.74 (1H, d, *J*=8.0 Hz, H-9 of benzoazepine), 7.1—7.6 (11H, m, Ar-H)	422
9	CN	Ph	75	241—244	$C_{32}H_{25}N_3O_2 \cdot 1/5H_2O$	1.9—2.2 (2H, m, azepine), 2.5—2.7 (1H, m, azepine), 2.8—3.0 (2H, m, azepine), 4.6—4.8 (1H, m, azepine), 5.55 (1H, s, C=CHCN), 6.68 (1H, d, *J*=7.2 Hz, H-9 of benzoazepine), 6.8—7.9 (16H, m, Ar-H)	484
10	CN	4-MePh	68	193—194	$C_{33}H_{27}N_3O_2 \cdot 1/2MeCN$	2.0—2.2 (2H, m, azepine), 2.36 (3H, s, Me), 2.8—3.0 (2H, m, azepine), 3.5—3.7 (1H, m, azepine), 4.6—4.8 (1H, m, azepine), 5.54 (1H, s, C=CHCN), 6.69 (1H, d, *J*=7.6 Hz, H-9 of benzoazepine), 6.9—7.9 (15H, m, Ar-H)	498
11	CO_2H	Me	23	169—172	$C_{27}H_{24}N_2O_4$	1.7—2.1 (2H, m, azepine), 2.47 (3H, s, Me), 3.0—3.6 (3H, m, azepine), 4.5—4.7 (1H, m, azepine), 6.06 (1H, s, C=CHCO), 6.71 (1H, d, *J*=6.7 Hz, H-9 of benzoazepine), 7.1—7.5 (11H, m, Ar-H)	441
14	CONHMe	Me	15	145—148	$C_{28}H_{27}N_3O_3 \cdot 1/2H_2O$	1.7—2.1 (2H, m, azepine), 2.47 (3H,s, MePh), 2.8—3.0 (1H, m, azepine), 2.92 (3H, d, *J*=4.8 Hz, NHMe), 3.2—3.6 (2H, m, azepine), 4.5—4.7 (1H, m, azepine), 5.65 (1H, d, *J*=4.8 Hz, NHMe), 5.91 (1H, s, C=CHCO), 6.69 (1H, d, *J*=6.7 Hz, H-9 of benzoazepine), 7.08 (1H, t, *J*=7.2 Hz, H-8 of benzoazepine), 7.2—7.5 (10H, m, Ar-H)	454
19	CONHMe	Ph	2.9	143—148	$C_{33}H_{29}N_3O_3 \cdot 3/2H_2O$	1.7—2.1 (2H, m, azepine), 2.8—3.0 (1H, m, azepine), 2.92 (3H, d, *J*=4.8 Hz, Me), 3.1—3.6 (2H, m, azepine), 4.5—4.7 (1H, m, azepine), 5.64(1H, d, *J*=4.6 Hz, NHMe), 5.85 (1H, s, C=CHCO), 6.63(1H, m, H-9 of benzoazepine), 6.8—7.9 (16H, m, Ar-H)	516
20	CONHMe	4-MePh	71	147—150	$C_{34}H_{31}N_3O_3 \cdot 1/2H_2O$	1.7—2.1 (2H, m, azepine), 2.37 (3H, s, MePh), 2.8—3.0 (4H, m, NHMe and azepine), 3.1—3.5 (2H, m, azepine), 4.5—4.7 (1H, m, azepine), 5.66 (1H, br, NHMe), 5.89 (1H, s, C=CHCO), 6.64 (1H, br, H-9 of benzoazepine), 6.9—7.9 (15H, m, Ar-H)	530
25		Ph	34	127—129	$C_{38}H_{32}N_4O_3 \cdot H_2O$	1.7—2.1 (2H, m, azepine), 2.9—3.6 (3H, m, azepine), 4.4—4.6 (1H, m, azepine), 4.67 (2H, d, *J*=5.2 Hz, $NHCH_2$), 6.04 (1H, s, C=CHCO), 6.63(1H, br, H-9 of benzoazepine), 6.7—7.9(19H, m, Ar-H), 8.71(1H, d, *J*=5.2 Hz, H-6 of pyridine)	593
27		Ph	32	115—120	$C_{37}H_{36}N_4O_3 \cdot H_2O \cdot 1/2AcOEt$	1.8—2.1 (2H, m, azepine), 2.32 (3H, s, Me), 2.3—2.5 (4H, m, piperazine), 3.4—3.6 (4H, m, piperazine), 3.7—3.8 (2H, m, azepine), 4.6—4.8 (1H, m, azepine), 6.18 (1H, s, C=CHCO), 6.63 (1H, m, H-9 of benzoazepine), 6.8—7.9 (16H, m, Ar-H)	585

a) Yields were based on the final step of the indicated synthetic method and were not optimized. *b*) Analytical results were within ±0.4% of the theoretical values unless otherwise noted.

Table 6. Physical and Spectral Data of *Endo*-Olefin Derivatives



No.	R_1	R_2	Yield (%)[a]	mp (°C)	Formula[b]	^{1}H-NMR (DMSO-d_6) δ	MS *m/z* (M^++1)
12	CO_2Et	Me	37	186—187	$C_{29}H_{28}N_2O_4$	1.14 (3H, t, *J*=6.8 Hz, $CH_2C\underline{H}_3$), 2.2—2.3 (1H, m, azepine), 2.34 (3H, s, Me<u>Ph</u>), 2.4—2.6 (1H, m, azepine), 3.3—3.4 (1H, m, azepine), 3.52 (1H, d, *J*=16 Hz, $C\underline{H}_2CO$), 3.93 (1H, d, *J*=16 Hz, $C\underline{H}_2CO$), 4.06 (2H, q, *J*=6.8 Hz, $C\underline{H}_2CH_3$), 4.5—4.7 (1H, m, azepine), 6.26 (1H, t, *J*=6.0 Hz, $C=C\underline{H}CH_2$), 6.72 (1H, d, *J*=7.6 Hz, H-9 of benzoazepine), 7.01 (1H, t, *J*=7.2 Hz, H-8 of benzoazepine), 7.2—7.6 (10H, m, Ar-H), 10.31 (1H, s, NH)	469
13	CO_2H	Me	61	>250	$C_{27}H_{24}N_2O_4 \cdot 1/3H_2O$	2.2—2.3 (1H, m, azepine), 2.34 (3H, s, Me), 2.4—2.6 (1H, m, azepine), 3.2—3.4 (1H, m, azepine), 3.44 (1H, d, *J*=16 Hz, $C\underline{H}_2CO$), 3.87 (1H, d, *J*=16 Hz, $C\underline{H}_2CO$), 4.5—4.7 (1H, m, azepine), 6.23 (1H, t, *J*=5.4 Hz, $C=C\underline{H}CH_2$), 6.71 (1H, d, *J*=7.6 Hz, H-9 of benzoazepine), 6.99 (1H, t, *J*=7.6 Hz, H-8 of benzoazepine), 7.2—7.6 (10H, m, Ar-H), 10.32 (1H, s, NH), 12.42 (1H, br, CO_2H)	441
15	CONHMe	Me	29	>250	$C_{28}H_{27}N_3O_3$	2.0—2.2 (1H, m, azepine), 2.33 (3H, s, Me<u>Ph</u>), 2.4—2.5 (1H, m, azepine), 2.57 (3H, d, *J*=4.9 Hz, NH<u>Me</u>), 3.22 (1H, d, *J*=15 Hz, $C\underline{H}_2CO$), 3.4—3.5 (1H, m, azepine), 3.60 (1H, d, *J*=15 Hz, $C\underline{H}_2CO$), 4.5—4.6 (1H, m, azepine), 6.20 (1H, t, *J*=6.0 Hz, $C=C\underline{H}CH_2$), 6.70 (1H, d, *J*=7.2 Hz, H-9 of benzoazepine), 6.98 (1H, t, *J*=7.6 Hz, H-8 of benzoazepine), 7.1—7.6 (10H, m, Ar-H), 7.94 (1H, d, *J*=3.9 Hz, N<u>H</u>Me), 10.29 (1H, s, N<u>H</u>Ph)	454
21	CONHMe	Ph	69	194—196	$C_{33}H_{29}N_3O_3 \cdot 1/2H_2O$	2.0—2.2 (1H, m, azepine), 2.3—2.5 (1H, m, azepine), 2.54 (3H, d, *J*=4.4 Hz, NH<u>Me</u>), 3.20 (1H, d, *J*=15 Hz, $C\underline{H}_2CO$), 3.4—3.5 (1H, m, azepine), 3.58 (1H, d, *J*=15 Hz, $C\underline{H}_2CO$), 4.4—4.6 (1H, m, azepine), 6.18 (1H, t, *J*=5.8 Hz, $C=C\underline{H}CH_2$), 6.67 (1H, d, *J*=7.6 Hz, H-9 of benzoazepine), 6.97 (1H, t, *J*=7.4 Hz, H-8 of benzoazepine), 7.0—7.6 (15H, m, Ar-H), 7.9—8.0 (1H, m, N<u>H</u>Me), 10.23 (1H, s, N<u>H</u>Ph)	516
22	CONHMe	4-MePh	55	194—196	$C_{34}H_{31}N_3O_3 \cdot H_2O$	2.0—2.2 (1H, m, azepine), 2.28 (3H, s, Me<u>Ph</u>), 2.3—2.5 (1H, m, azepine), 2.55 (3H, d, *J*=5.2 Hz, NH<u>Me</u>), 3.20 (1H, d, *J*=15 Hz, $C\underline{H}_2CO$), 3.4—3.5 (1H, m, azepine), 3.59 (1H, d, *J*=15 Hz, $C\underline{H}_2CO$), 4.4—4.6 (1H, m, azepine), 6.18 (1H, t, *J*=6.2 Hz, $C=C\underline{H}CH_2$), 6.68 (1H, d, *J*=8.0 Hz, H-9 of benzoazepine), 6.97 (1H, t, *J*=7.4 Hz, H-8 of benzoazepine), 7.0—7.6 (14H, m, Ar-H), 7.9—8.0 (1H, m, N<u>H</u>Me), 10.24 (1H, s, N<u>H</u>Ph)	530
26		Ph	39	187—189	$C_{38}H_{32}N_4O_3 \cdot HCl \cdot 2H_2O$[c]	2.1—2.3 (1H, m, azepine), 2.4—2.6 (1H, m, azepine), 3.37 (1H, d, *J*=15 Hz, $C\underline{H}_2CO$), 3.4—3.5 (1H, m, azepine), 3.77 (1H, d, *J*=15 Hz, $C\underline{H}_2CO$), 4.44 (2H, d, *J*=6.0 Hz, $NHC\underline{H}_2$), 4.5—4.6 (1H, m, azepine), 6.25 (1H, t, *J*=5.4 Hz, $C=C\underline{H}CH_2$), 6.68 (1H, d, *J*=7.2 Hz, H-9 of benzoazepine), 6.99 (1H, t, *J*=7.4 Hz, H-8 of benzoazepine), 7.0—7.9 (18H, m, Ar-H), 8.55 (1H, d, *J*=4.8 Hz, H-6 of pyridine), 10.23 (1H, s, N<u>H</u>Ph)	593
28		Ph	32	>250	$C_{37}H_{36}N_4O_3 \cdot HCl \cdot H_2O$	2.1—2.3 (1H, m, azepine), 2.4—2.6 (1H, m, azepine), 2.74 (3H, s, Me), 2.9—3.7 (7H, m, piperazine, $C\underline{H}_2CO$, and azepine), 3.8—4.3 (4H, m, piperazine), 4.4—4.6 (1H, m, azepine), 6.14 (1H, m, $C=C\underline{H}CH_2$), 6.67 (1H, d, *J*=7.6 Hz, H-9 of benzoazepine), 6.98 (1H, m, H-8 of benzoazepine), 7.0—7.6 (15H, m, Ar-H), 10.30 (1H, s, NH)	585

a, *b*) See footnotes in Table 5. *c*) H (Calcd 5.75. Found 5.30).

Compounds **4b** and **4c** were synthesized in the same manner.

4′-(5-Oxo-2,3,4,5-tetrahydro-1*H*-1-benzoazepine-1-carbonyl)-2-phenylbenzanilide (4b) Colorless powder, mp 175—178 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.0—2.2 (2H, m, azepine), 2.8—2.9 (2H, m, azepine), 3.3—3.4 (1H, m, azepine), 4.4—4.7 (1H, m, azepine), 6.69 (1H, d, J=7.6 Hz, H-9 of benzoazepine), 6.8—7.9 (16H, m, Ar-H). FAB-MS *m/z*: 461 (M^++1). *Anal*. Calcd for $C_{30}H_{24}N_2O_3$: C, 78.24; H, 5.25; N, 6.08. Found: C, 78.37; H, 5.51; N, 6.07.

2-(4-Methyl)phenyl-4′-(5-oxo-2,3,4,5-tetrahydro-1*H*-1-benzoazepine-1-carbonyl)benzanilide (4c) Colorless powder, mp 181—182 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.0—2.2 (2H, m, azepine), 2.35 (3H, s, Me), 2.88(2H, m, azepine), 3.4—3.6 (1H, m, azepine), 4.0—4.2 (1H, m, azepine), 6.71 (1H, d, J=8.0 Hz, H-9 of benzoazepine), 6.8—7.9 (15H, m, Ar-H). FAB-MS *m/z*: 475 (M^++1). *Anal*. Calcd for $C_{31}H_{26}N_2O_3$: C, 78.46; H, 5.52; N, 5.90. Found: C, 78.17; H, 5.55; N, 5.86.

(*E*)-4′-(5-Methoxymethylidene-2,3,4,5-tetrahydro-1*H*-1-benzoazepine-1-carbonyl)-2-methylbenzanilide (5a) and (*Z*)-4′-(5-Methoxymethylidene-2,3,4,5-tetrahydro-1*H*-1-benzoazepine-1-carbonyl)-2-methylbenzanilide (5b) Potassium *tert*-butoxide (3.93 g) was added to an ice-cooled solution of (methoxymethyl)triphenylphosphonium chloride (10.3 g) in THF (250 ml), and the mixture was stirred for 1 h. To this mixture was added **4a** (4.0 g) and the whole was stirred for 4 h at room temperature. It was then poured into ice-water, and the whole was extracted with ethyl acetate (AcOEt). The organic layer was washed with brine, dried, and concentrated. The residue was chromatographed over silica gel using 1 : 3 AcOEt–hexane and crystallized from Et_2O to give **5a** (1.83 g, 43%) and **5b** (330 mg, 7.7%).

5a: Colorless powder, mp 201—204 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.7—1.8 (1H, m, azepine), 1.9—2.0 (1H, m, azepine), 2.3—2.4 (1H, m, azepine), 2.47 (3H, s, MePh), 2.8—2.9 (1H, m, azepine), 3.0—3.1 (1H, m, azepine), 3.77 (3H, s, MeO), 4.7—4.8 (1H, m, azepine), 6.25 (1H, s, C=CHOMe), 6.65 (1H, d, J=8.0 Hz, H-9 of benzoazepine), 6.95 (1H, t, J=7.5 Hz, H-8 of benzoazepine), 7.1—7.5 (10H, m, Ar-H). FAB-MS *m/z*: 427 (M^++1). *Anal*. Calcd for $C_{27}H_{26}N_2O_3 \cdot 1/2H_2O$: C, 74.46; H, 6.25; N, 6.43. Found: C, 74.56; H, 6.44; N, 6.05.

5b: Colorless powder, mp 243—247 °C. ^{1}H-NMR($CDCl_3$) δ: 1.8—2.0 (2H, m, azepine), 2.1—2.2 (1H, m, azepine), 2.4—2.5 (1H, m, azepine), 2.47 (3H, s, MePh), 2.8—2.9 (1H, m, azepine), 3.64 (3H, s, MeO), 4.9—5.1 (1H, m, azepine), 6.19 (1H, s, C=CHOMe), 6.68 (1H, d, J=7.6 Hz, H-9 of benzoazepine), 6.94 (1H, t, J=7.2 Hz, H-8 of benzoazepine), 7.1—7.5 (10H, m, Ar-H). FAB-MS *m/z*: 427 (M^++1). *Anal*. Calcd for $C_{27}H_{26}N_2O_3 \cdot 1/2H_2O$: C, 74.46; H, 6.25; N, 6.43. Found: C ,74.68; H, 6.22; N 6.29.

(*E*)-4′-(5-Benzylidene-2,3,4,5-tetrahydro-1*H*-1-benzoazepine-1-carbonyl)-2-methylbenzanilide (6) Potassium *tert*-butoxide (590 mg) was added to an ice-cooled solution of benzyltriphenylphosphonium chloride (1.79 g) in THF (40 ml), and the mixture was stirred for 1 h. To this mixture was added **4a** (600 mg) and the whole was stirred for 2 d at reflux temperature. It was then poured into ice-water, and the whole was extracted with AcOEt. The organic layer was washed with brine, dried, and concentrated. The residue was chromatographed over silica gel using 1 : 3 AcOEt–hexane and crystallized from Et_2O–hexane to give **6** (270 mg, 38%) as a colorless powder, mp 120—124 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.8—2.2 (2H, m, azepine), 2.46 (3H, s, Me), 2.5—2.7 (1H, m, azepine), 3.0—3.3 (2H, m, azepine), 4.7—4.9 (1H, m, azepine), 6.71 (1H, s, C=CHPh), 7.0—7.5 (17H, m, Ar-H). FAB-MS *m/z*: 473 (M^++1). *Anal*. Calcd for $C_{32}H_{28}N_2O_2$: C, 81.33; H, 5.97; N, 5.93. Found: C ,81.21; H, 5.95; N 5.83.

Ethyl (*E*)-{1-[4-(2-Methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzoazepin-5-ylidene}acetate (7) A suspension of 60% sodium hydride in mineral oil (1.0 g) in THF (120 ml) was cooled on ice, then triethyl phosphonoacetate (5.6 g) was added, and the mixture was stirred for 1 h. To this mixture was added **4a** (2.0 g) and the whole was stirred for 18 h at room temperature. It was then poured into ice-water, and the whole was extracted with AcOEt. The organic layer was washed with brine, dried, and concentrated. The residue was chromatographed over silica gel using 1 : 1 AcOEt–hexane and recrystallized from MeCN–Et_2O to give **7** (76 mg, 3.2%) as a colorless powder, mp 143—145 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.34 (3H, t, J=7.3 Hz, CH_2CH_3), 1.7—2.2 (2H, m, azepine), 2.44 (3H, s, Me), 2.9—3.5 (3H, m, azepine), 4.24 (2H, q, J=6.7 Hz, CH_2CH_3), 4.4—4.6 (1H, m, azepine), 6.04(1H, s, C=CHCO), 6.67 (1H, d, J=6.1 Hz, H-9 of benzoazepine), 7.0—7.5 (11H, m, Ar-H). FAB-MS *m/z*: 469 (M^++1). *Anal*. Calcd for $C_{29}H_{28}N_2O_4 \cdot 1/3H_2O$: C, 73.40; H, 6.09; N, 5.90. Found: C, 73.36; H, 5.89; N, 5.90.

Compounds **8**—**10** were synthesized in the same manner.

Hydrolysis of 7 with NaOH A mixture of **7** (200 mg) in ethanol (EtOH) (1 ml) was added to a solution of NaOH (20 mg) in water (1 ml), and the mixture was stirred for 18 h at room temperature. It was then concentrated and the residue was dissolved in water. This was treated with 1 N HCl and the resulting precipitate was collected by filtration and washed with water. It was found to be almost a 1 : 1 mixture of **11** and **13** from HPLC analysis using 1 : 1 MeCN–0.01 M KH_2PO_4 buffer as eluent and UV monitoring (254 nm).

(*E*)-{1-[4-(2-Methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzoazepin-5-ylidene}acetic Acid (11) A mixture of **7** (200 mg) in acetic acid (AcOH) (5 ml) and concentrated HCl (2 ml) was stirred for 24 h at 50 °C. It was poured into ice-water, and the resulting precipitate was collected by filtration and washed with water. It was found to be almost a 7 : 1 mixture of **11** and **13** from HPLC analysis using 1 : 1 MeCN–0.01 M KH_2PO_4 buffer as eluent and UV monitoring (254 nm). It was recrystallized from AcOEt–Et_2O to give **11** (50 mg, 23%) as a colorless powder, mp 169—172 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.7—2.1 (2H, m, azepine), 2.47 (3H, s, Me), 3.0—3.6 (3H, m, azepine), 4.5—4.7 (1H, m, azepine), 6.06 (1H, s, C=CHCO), 6.71 (1H, d, J=6.7 Hz, H-9 of benzoazepine), 7.1—7.5 (11H, m, Ar-H). FAB-MS *m/z*: 441 (M^++1). *Anal*. Calcd for $C_{27}H_{24}N_2O_4$: C, 71.43; H, 5.66; N, 6.17. Found: C, 71.49; H, 5.89; N, 5.83.

Ethyl {1-[4-(2-Methylbenzoylamino)benzoyl]-2,3-dihydro-1*H*-1-benzoazepin-5-yl}acetate (12) K_2CO_3 (30 mg) was added to a solution of **7** (200 mg) in EtOH (20 ml), and the mixture was stirred for 2 h at reflux temperature. It was concentrated and the residue was extracted with AcOEt. The organic layer was washed with brine, dried, and concentrated. It was found to be almost a 1 : 2 mixture of **7** and **12** from HPLC analysis using 1 : 1 MeCN–0.01 M KH_2PO_4 buffer as eluent and UV monitoring (254 nm). The residue was chromatographed over silica gel using 1 : 1 AcOEt–hexane and crystallized from Et_2O to give **12** (74 mg, 37%) as a colorless powder, mp 186—187 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.14 (3H, t, J=6.8 Hz, CH_2CH_3), 2.2—2.3 (1H, m, azepine), 2.34 (3H, s, MePh) 2.4—2.6 (1H, m, azepine), 3.3—3.4 (1H, m, azepine), 3.52 (1H, d, J=16 Hz, CH_2CO), 3.93 (1H, d, J=16 Hz, CH_2CO), 4.06 (2H, q, J=6.8 Hz, CH_2CH_3), 4.5—4.7 (1H, m, azepine), 6.26 (1H, t, J=6.0 Hz, C=CHCH$_2$), 6.72 (1H, d, J=7.6 Hz, H-9 of benzoazepine), 7.01 (1H, t, J=7.2 Hz, H-8 of benzoazepine), 7.2—7.6 (10H, m, Ar-H), 10.31 (1H, s, NH). FAB-MS *m/z*: 469 (M^++1). *Anal*. Calcd for $C_{29}H_{28}N_2O_4$: C, 74.34; H, 6.02; N, 5.98. Found: C, 74.41; H, 6.07; N, 5.94.

{1-[4-(2-Methylbenzoylamino)benzoyl]-2,3-dihydro-1*H*-1-benzoazepin-5-yl}acetic Acid (13) A mixture of **12** (173 mg) in AcOH (5 ml) and concentrated HCl (2 ml) was stirred for 4 h at 50 °C. It was poured into ice-water, and the resulting precipitate was collected by filtration and washed with water. It was recrystallized from AcOEt to give **13** (100 mg, 61%) as a colorless powder, mp >250 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.2—2.3 (1H, m, azepine), 2.34 (3H, s, Me), 2.4—2.6 (1H, m, azepine), 3.2—3.4 (1H, m, azepine), 3.44 (1H, d, J=16 Hz, CH_2CO), 3.87 (1H, d, J=16 Hz, CH_2CO), 4.5—4.7 (1H, m, azepine), 6.23 (1H, t, J=5.4 Hz, C=CHCH$_2$), 6.71 (1H, d, J=7.6 Hz, H-9 of benzoazepine), 6.99 (1H, t, J=7.6 Hz, H-8 of benzoazepine), 7.2—7.6 (10H, m, Ar-H), 10.32 (1H, s, NH), 12.42 (1H, br, CO_2H). FAB-MS *m/z*: 441 (M^++1). *Anal*. Calcd for $C_{27}H_{24}N_2O_4 \cdot 1/3H_2O$: C, 72.63; H, 5.57; N, 6.27. Found: C, 72.45; H, 5.67; N, 6.14.

(*E*)-*N*-Methyl-{1-[4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzoazepin-5-ylidene}acetamide (14) and *N*-Methyl-{1-[4-(2-methylbenzoylamino)benzoyl]-2,3-dihydro-1*H*-1-benzoazepin-5-yl}acetamide (15) A mixture of **7** (400 mg) and a solution of 40% methylamine in methanol (MeOH) (6 ml) was stirred for 6 h at 50 °C in a sealed tube. It was found to be almost a 1 : 3 mixture of **14** and **15** from HPLC analysis using 1 : 1 MeCN–0.01 M KH_2PO_4 buffer as eluent and UV monitoring (254 nm). After cooling, the resulting precipitate was collected by filtration and washed with MeOH, then recrystallized from $CHCl_3$ to give **15** (130 mg, 29%) as a colorless powder, mp >250 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.0—2.2 (1H, m, azepine), 2.33 (3H, s, MePh), 2.4—2.5 (1H, m, azepine), 2.57 (3H, d, J=4.9 Hz, NHMe), 3.22(1H, d, J=15 Hz, CH_2CO), 3.4—3.5(1H, m, azepine), 3.60 (1H, d, J=15 Hz, CH_2CO), 4.5—4.6 (1H, m, azepine), 6.20 (1H, t, J=6.0 Hz, C=CHCH$_2$), 6.70 (1H, d, J=7.2 Hz, H-9 of benzoazepine), 6.98 (1H, t, J=7.6 Hz, H-8 of benzoazepine), 7.1—7.6 (10H, m, Ar-H), 7.94 (1H, d, J=3.9 Hz, NHMe), 10.29 (1H, s, NHPh). FAB-MS *m/z*: 454 (M^++1). *Anal*. Calcd for $C_{28}H_{27}N_3O_3$: C, 74.15; H, 6.00; N, 9.26. Found: C, 73.84; H, 5.98; N, 9.31. The mother liquid was concentrated and chromatographed over silica gel using 1:3 AcOEt–hexane and recrystallized from AcOEt–hexane to give **14** (70 mg, 15%) as a colorless powder, mp 145—148 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.7—2.1 (2H, m, azepine), 2.47 (3H, s, MePh), 2.8—3.0 (1H, m, azepine), 2.92 (3H, d, J=4.8 Hz, NHMe), 3.2—3.6 (2H, m, azepine), 4.5—4.7 (1H, m, azepine), 5.65 (1H, d, J=4.8 Hz, NHMe), 5.91 (1H, s, C=CHCO), 6.69 (1H, d, J=6.7 Hz, H-9 of benzo-

azepine), 7.08 (1H, t, J=7.2 Hz, H-8 of benzoazepine), 7.2—7.5 (10H, m, Ar-H). FAB-MS m/z: 454 (M^++1). *Anal*. Calcd for $C_{28}H_{27}N_3O_3 \cdot 1/2H_2O$: C, 72.71; H, 6.10; N, 9.08. Found: C, 73.00; H, 6.14; N, 8.93.

Isomerization of 14 K_2CO_3 (5 mg) was added to a solution of **14** (20 mg) in EtOH (2 ml), and the mixture was stirred for 10 h at reflux temperature. It was found to be almost a 1 : 1 mixture of **14** and **15** from HPLC analysis using 1 : 1 MeCN–0.01 M KH_2PO_4 buffer as eluent and UVmonitoring (254 nm).

(*E*)-[1-(4-Aminobenzoyl)-2,3,4,5-tetrahydro-1*H*-1-benzoazepin-5-ylidene]-*N*-methylacetamide (17) and [1-(4-Aminobenzoyl)-2,3-dihydro-1*H*-1-benzoazepin-5-yl]-*N*-methylacetamide (18) A suspension of 60% sodium hydride in mineral oil (3.42 g) in THF (350 ml) was cooled on ice, then triethyl phosphonoacetate (19.2 g, 5 eq) was added, and the mixture was stirred for 30 min. To this mixture was added **2** (4.8 g) and the whole was stirred for 18 h at room temperature. It was then poured into ice-water, and the whole was extracted with AcOEt. The organic layer was washed with brine, dried, and concentrated. The residue was chromatographed over silica gel using $CHCl_3$ to remove excess reagent and crystallized from AcOEt–Et_2O to give a mixture of ethyl [1-(4-aminobenzoyl)-2,3,4,5-tetrahydro-1*H*-1-benzoazepin-5-ylidene]acetate and ethyl [1-(4-aminobenzoyl)-2,3-dihydro-1*H*-1-benzoazepin-5-yl]acetate (**16**) (1.3 g, 22%). A mixture of **16** (1.3 g) and a solution of 40% methylamine in MeOH (6 ml) was stirred for 9 h at 50 °C in a sealed tube. It was concentrated and the residue was recrystallized from $CHCl_3$ to give **18** (220 mg, 18%) as a colorless powder, mp 206—209 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.0—2.2 (1H, m, azepine), 2.3—2.5 (1H, m, azepine), 2.55 (3H, d, J=4.8 Hz, Me), 3.19 (1H, d, J=14 Hz, C$\underline{H}_2$CO), 3.3—3.5 (1H, m, azepine), 3.55 (1H, d, J=14 Hz, C$\underline{H}_2$CO), 4.4—4.6 (1H, m, azepine), 5.36 (2H, s, NH_2), 6.17 (1H, t, J=6.2 Hz, C=C$\underline{H}$CH$_2$), 6.22 (2H, d, J=8.8 Hz, H-2,6 of benzoyl), 6.65 (1H, d, J=7.6 Hz, H-9 of benzoazepine), 6.85 (2H, d, J=8.4 Hz, H-3,5 of benzoyl), 6.97 (1H, t, J=7.6 Hz, H-8 of benzoazepine), 7.17 (1H, t, J=7.4 Hz, H-7 of benzoazepine), 7.45 (1H, d, J=8.0 Hz, H-6 of benzoazepine), 7.85 (1H, d, J=4.4 Hz, N$\underline{H}$Me). FAB-MS m/z: 336 (M^++1). *Anal*. Calcd for $C_{20}H_{21}N_3O_2 \cdot 1/5H_2O$: C, 70.86; H, 6.36; N, 12.40. Found: C, 71.02; H, 6.34; N, 12.19. The mother liquid was concentrated and chromatographed over silica gel using 5 : 1 $CHCl_3$–acetone and crystallized from AcOEt–hexane to give **17** (50 mg, 4.0%) as a colorless powder, mp 102—107 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.8—2.0 (2H, m, azepine), 2.90 (3H, d, J=4.8 Hz, Me), 3.0—3.3 (2H, m, azepine), 3.76 (2H, s, NH_2), 5.67(1H, br, N$\underline{H}$Me), 5.91(1H, s, C=C$\underline{H}$CO), 6.37(2H, d, J=8.8 Hz, H-2,6 of benzoyl), 6.69 (1H, d, J=7.6 Hz, H-9 of benzoazepine), 7.02 (2H, d, J=8.3 Hz, H-3,5 of benzoyl), 7.06 (1H, t, J=7.7 Hz, H-8 of benzoazepine), 7.17 (1H, t, J=7.5 Hz, H-7 of benzoazepine), 7.26 (1H, d, J=7.6 Hz, H-6 of benzoazepine). FAB-MS m/z: 336 (M^++1). *Anal*. Calcd for $C_{20}H_{21}N_3O_2 \cdot 1/2$AcOEt: C, 69.64; H, 6.64; N, 11.07. Found: C, 69.72; H, 6.80; N, 11.53.

(*E*)-*N*-Methyl-{1-[4-(2-phenylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzoazepin-5-ylidene}acetamide (19) To an ice-cooled solution of 2-phenylbenzoic acid (130 mg) in CH_2Cl_2 (2 ml) were added a catalytic amount of *N*,*N*-dimethylformamide (DMF) and oxalyl chloride (90 μl), and the mixture was stirred for 4 h at room temperature. It was concentrated and the residue was dissolved in CH_2Cl_2 (2 ml). This solution was added dropwise to an ice-cooled solution of **17** (220 mg) in pyridine (10 ml) and the mixture was stirred for 18 h at room temperature. It was then poured into water, and the whole was extracted with $CHCl_3$. The organic layer was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine, dried, and concentrated. The residue was chromatographed over silica gel using 5 : 1 AcOEt–hexane and crystallized from Et_2O to give **19** (10 mg, 2.9%) as a colorless powder, mp 143—148 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.7—2.1 (2H, m, azepine), 2.8—3.0 (1H, m, azepine), 2.92 (3H, d, J=4.8 Hz, Me), 3.1—3.6 (2H, m, azepine), 4.5—4.7 (1H, m, azepine), 5.64 (1H, d, J=4.6 Hz, N$\underline{H}$Me), 5.85 (1H, s, C=C$\underline{H}$CO), 6.63(1H, m, H-9 of benzoazepine), 6.8—7.9 (16H, m, Ar-H). FAB-MS m/z: 516 (M^++1). *Anal*. Calcd for $C_{33}H_{29}N_3O_3 \cdot 3/2H_2O$: C, 73.04; H, 5.94; N, 7.74. Found: C, 72.80; H, 5.55; N, 7.42.

Compounds **20**—**22** were synthesized in the same manner.

(*E*)-{1-[4-(2-Phenylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzoazepin-5-ylidene}-*N*-(2-pyridylmethyl)acetamide (25) and {1-[4-(2-Phenylbenzoylamino)benzoyl]-2,3-dihydro-1*H*-1-benzoazepin-5-yl}-*N*-(2-pyridylmethyl)acetamide monohydrochloride (26) To an ice-cooled solution of 2-phenylbenzoic acid (198 mg) in CH_2Cl_2 (3 ml) were added a catalytic amount of DMF and oxalyl chloride (135 μl), and the mixture was stirred for 3 h at room temperature. It was then concentrated and the residue was dissolved in CH_2Cl_2 (3 ml). This solution was added dropwise to an ice-cooled solution of **16** (350 mg) in pyridine (7 ml) and the mixture was stirred for 18 h at room temperature. It was poured into water, and the whole was extracted with $CHCl_3$. The organic layer was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine, dried, and concentrated. The residue was crystallized from AcOEt–Et_2O to give a mixture of ethyl {1-[4-(2-phenylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzoazepin-5-ylidene}acetate and ethyl {1-[4-(2-phenylbenzoylamino)benzoyl]-2,3-dihydro-1*H*-1-benzoazepin-5-yl}acetate (**23**) (337 mg, 64%). The mixture of **23** (300 mg) and 1 N NaOH (2 ml) in EtOH (10 ml) was stirred for 14 h at room temperature. It was then concentrated, and the residue was acidicified with 1 N HCl. The resulting precipitate was collected by filtration and washed with water to give a mixture of {1-[4-(2-phenylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzoazepin-5-ylidene}acetic acid and {1-[4-(2-phenylbenzoylamino) benzoyl]-2,3-dihydro-1*H*-1-benzoazepin-5-yl}acetic acid (**24**) (238 mg, 84%). The mixture of **24** (200 mg), 2-(aminomethyl)pyridine (44 mg), 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide monohydorochloride (78 mg), and 1-hydroxybenzotriazole (55 mg) in THF (20 ml) was stirred for 10 h at room temperature. It was then poured into water, and the whole was extracted with AcOEt. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried, and concentrated. The residue was chromatographed over silica gel using 40 : 1 AcOEt–MeOH and recrystallized from AcOEt–hexane to give **25** (80 mg, 34%) and the free amine of **26** (116 mg, 49%). The free amine of **26** (100 mg) was dissolved in $CHCl_3$–MeOH, and to this solution was added a solution of 4 N HCl in AcOEt (50 μl) at 0—5 °C. The resulting precipitate was collected by filtration and washed with $CHCl_3$–MeOH to give **26** (85 mg, 39%).

25: Colorless powder, mp 127—129 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.7—2.1 (2H, m, azepine), 2.9—3.6 (3H, m, azepine), 4.4—4.6 (1H, m, azepine), 4.67 (2H, d, J=5.2 Hz, NH$\underline{C}$H$_2$), 6.04 (1H, s, C=C$\underline{H}$CO), 6.63 (1H, br, H-9 of benzoazepine), 6.7—7.9 (19H, m, Ar-H), 8.71 (1H, d, J=5.2 Hz, H-6 of pyridine). FAB-MS m/z: 593 (M^++1). *Anal*. Calcd for $C_{38}H_{32}N_4O_3 \cdot H_2O$: C, 74.74; H, 5.61; N, 9.17. Found: C, 75.04; H, 5.42; N, 9.07.

26: Colorless powder, mp 187—189 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.1—2.3 (1H, m, azepine), 2.4—2.6 (1H, m, azepine), 3.37 (1H, d, J=15 Hz, C$\underline{H}_2$CO), 3.4—3.5 (1H, m, azepine), 3.77 (1H, d, J=15 Hz, C$\underline{H}_2$CO), 4.44 (2H, d, J=6.0 Hz, NHC$\underline{H}_2$), 4.5—4.6 (1H, m, azepine), 6.25 (1H, t, J=5.4 Hz, C=C$\underline{H}$CH$_2$), 6.68 (1H, d, J=7.2 Hz, H-9 of benzoazepine), 6.99 (1H, t, J=7.4 Hz, H-8 of benzoazepine), 7.0—7.9 (18H, m, Ar-H), 8.55 (1H, d, J=4.8 Hz, H-6 of pyridine), 10.23 (1H, s, N$\underline{H}$Ph). FAB-MS m/z: 593 (M^++1). *Anal*. Calcd for $C_{38}H_{32}N_4O_3 \cdot HCl \cdot 2H_2O$: C, 68.51; H, 5.75; N, 8.41; Cl, 5.32. Found: C, 68.18; H, 5.30; N, 8.35; Cl, 5.40.

Compounds **27** and **28** were synthesized in the same manner.

Ethyl {1-[4-(2-Methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzoazepin-5-yl}acetate (29) A mixture of **7** (1.46 g) and 10% Palladium–Carbon (150 mg) in EtOH (70 ml) was stirred under hydrogen atmosphere (1 atm) at room temperature. After absorption of 70 ml of hydrogen, the catalyst was removed by filtration, and the filtrate was concentrated. The residue was chromatographed over silica gel using 20 : 1 $CHCl_3$–acetone and crystallized from Et_2O to give **29** (704 mg, 48%) as a colorless powder, mp 175—176 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.1—1.3 (3H, m, CH$_2$C$\underline{H}_3$), 1.3—2.2 (4H, m, azepine), 2.45 (3H, s, M$\underline{e}$Ph), 2.6—3.3 (3H, m, C$\underline{H}_2$CO and azepine), 3.5—3.8 (1H, m, azepine), 4.0—4.3 (2H, m, C$\underline{H}_2$CH$_3$), 4.4—4.6 (0.8H, m, azepine), 5.1—5.2 (0.2H, m, azepine), 6.5—6.8 (1H, m, H-9 of benzoazepine), 6.9—7.1 (1H, m, H-8 of benzoazepine), 7.1—7.5 (10H, m, Ar-H). FAB-MS m/z: 471 (M^++1). *Anal*. Calcd for $C_{29}H_{30}N_2O_4$: C, 74.02; H, 6.43; N, 5.95. Found: C, 73.95; H, 6.52; N, 6.00.

***N*-Methyl-{1-[4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzoazepin-5-yl}acetamide (30)** A mixture of **29** (150 mg) and a solution of 40% methylamine in MeOH (4 ml) was stirred for 8 h at 50 °C in a sealed tube. The resulting precipitate was collected by filtration and washed with MeOH, then recrystallized from $CHCl_3$ to give **30** (110 mg, 76%) as a colorless powder, mp >250 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.2—2.3 (4H, m, azepine), 2.41 (3H, s, M$\underline{e}$Ph), 2.65 (3H, br, NH$\underline{Me}$), 2.6—3.2 (3H, m, C$\underline{H}_2$CO and azepine), 3.5—3.9 (1H, m, azepine), 4.4—4.6 (0.8H, m, azepine), 5.0—5.2 (0.2H, m, azepine), 6.5—6.7 (1H, m, H-9 of benzoazepine), 6.9—7.0 (1H, m, H-8 of benzoazepine), 7.1—7.6 (10H, m, Ar-H), 7.85 (1H, br, N$\underline{H}$Me), 10.10 (0.8H, s, N$\underline{H}$Ph), 10.16 (0.2H, s, N$\underline{H}$Ph). FAB-MS m/z: 456 (M^++1). *Anal*. Calcd for $C_{28}H_{29}N_3O_3 \cdot 1/2H_2O$: C, 72.39; H, 6.51; N, 9.05. Found: C, 72.15; H, 6.36; N, 8.92.

Ethyl {5-[4-(2-Methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-1-yl}acetate (32) **3a** (390 mg) was added to an ice-cooled solution of ethyl 5-[(4-aminobenzoyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-1-yl]acetate (**31**)[11] (900 mg) and Et_3N (260 mg) in CH_2Cl_2 (20 ml), and the mixture was stirred for 30 min at room temperature. The mixture was washed with water and brine, dried, and concentrated. The

residue was recrystallized from AcOEt to give **32** (1010 mg, 84%) as a colorless powder, mp 181—185 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, t, J=7.1 Hz, $CH_2C\underline{H}_3$), 1.9—2.0 (1H, m, diazepine), 2.1—2.2 (1H, m, diazepine), 2.47 (3H, s, Me-Ph), 3.0—3.3 (2H, m, diazepine), 3.6—3.7 (1H, m, diazepine), 4.01 (1H, d, J=17 Hz, $C\underline{H}_2CO$), 4.13 (1H, d, J=17 Hz, $C\underline{H}_2CO$), 4.26 (2H, q, J=7.1 Hz, $CH_2C\underline{H}_3$), 4.6—4.7 (1H, m, diazepine), 6.5—6.6 (2H, m, Ar-H), 6.70 (1H, d, J=8.2 Hz, H-9 of benzodiazepine), 7.0—7.5 (9H, m, Ar-H). FAB-MS *m/z*: 472 (M^++1). *Anal*. Calcd for $C_{28}H_{29}N_3O_4 \cdot 1/2H_2O$: C, 69.98; H, 6.29; N, 8.74. Found: C, 70.12; H, 6.35; N, 8.82.

***N*-Methyl-{5-[4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-1-yl}acetamide (33)** A mixture of **32** (200 mg) and a solution of 40% methylamine in MeOH (3 ml) was stirred for 5 h at 50 °C in a sealed tube. It was then concentrated and the resulting precipitate was collected by filtration and washed with AcOEt to give **33** (130 mg, 66%) as a colorless powder, mp 199—204 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.8—1.9 (1H, m, diazepine), 2.0—2.1 (1H, m, diazepine), 2.34 (3H, s, Me-Ph), 2.66 (3H, d, J=4.9 Hz, NH-Me), 3.0—3.2 (2H, m, diazepine), 3.6—3.7 (1H, m, diazepine), 3.83 (1H, d, J=17 Hz, $C\underline{H}_2CO$), 3.95 (1H, d, J=17 Hz, $C\underline{H}_2CO$), 4.5—4.6 (1H, m, diazepine), 6.5—6.6 (2H, m, Ar-H), 6.82 (1H, d, J=7.8 Hz, H-9 of benzodiazepine), 7.0—7.6 (9H, m, Ar-H), 7.91 (1H, d, J=4.9 Hz, N-H-Me), 10.31 (1H, s, N-H-Ph). FAB-MS *m/z*: 457 (M^++1). *Anal*. Calcd for $C_{27}H_{28}N_4O_3 \cdot H_2O$: C, 68.48; H, 6.17; N, 11.83. Found: C, 68.08; H, 6.17; N, 11.66.

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References and Notes

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13) It was found that there was a relationship between the V_2 receptor binding affinity potential of some compounds for rat kidney and for rabbit kidney in our investigation (data not shown).
14) Experimental method described in reference (11).