Nonpeptide Arginine Vasopressin Antagonists for Both V_{1A} and V_2 Receptors: Synthesis and Pharmacological Properties of 4′-(1,4,5,6-Tetrahydroimidazo[4,5-*d*][1]benzoazepine-6-carbonyl)benzanilide Derivatives and 4′-(5,6-Dihydro-4*H*-thiazolo[5,4-*d*][1]benzoazepine-6-carbonyl)benzanilide Derivatives

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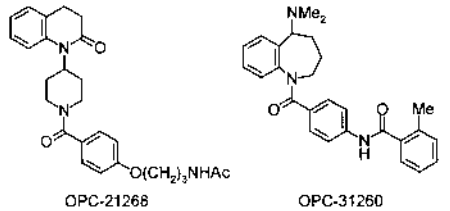
Arginine vasopressin (AVP) has a dual action mainly in the periphery, *i.e.*, vasoconstriction and water reabsorption *via* V_{1A} and V_2 receptors; it may play a role in a number of diseases, including congestive heart failure (CHF), hypertension, renal disease, edema, and hyponatremia. We have attempted to develop a new series of orally active 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′-(1,4,5,6-tetrahydroimidazo[4,5-*d*][1]benzoazepine-6-carbonyl)benzanilide and 4′-(5,6-dihydro-4*H*-thiazolo[5,4-*d*][1]benzoazepine-6-carbonyl)benzanilide were synthesized and examined for AVP antagonist activity for both V_{1A} and V_2 receptors. As a result, it was found that the 4′-(1,4,5,6-tetrahydroimidazo[4,5-*d*][1]benzoazepine-6-carbonyl)-2-phenylbenzanilide derivatives showed potent binding affinity for both V_{1A} and V_2 receptors. Especially, 4′-(2-methyl-1,4,5,6-tetrahydroimidazo[4,5-*d*][1]benzoazepine-6-carbonyl)-2-phenylbenzanilide monohydrochloride (18, YM087=conivaptan hydrochloride) exhibited potent binding affinity and AVP antagonist activity, after intravenous administration, for both V_{1A} and V_2 receptors. Furthermore, YM087 exhibited the most potent oral activity for the V_2 receptor. Details of the synthesis and pharmacological properties of this series are presented.

Key words YM087; conivaptan hydrochloride; arginine vasopressin antagonist; congestive heart failure; benzoazepine; 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 exhibits many actions in the periphery *via* V_{1A} and V_2 receptors. In particular, the main dual action, *i.e.*, vasoconstriction and water reabsorption, 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 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 orally available 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 4′-[5-(substituted methylidene)-2,3,4,5-tetrahydro-1*H*-1-benzoazepine-1-carbonyl]benzanilide derivatives (**1**, Fig. 2). From the results of structure–activity relationships, it was suggested that fixing the orientation of the substituent to the entgegen site by introduction of the alkylidene group at the 5-position of benzoazepine was effective in increasing the binding affinity potentials for both V_{1A} and V_2 receptors. This suggestion was supported by the results of 5-(substituted alkylidene)-4,4-difluoro-2,3,4,5-tetrahydro-1*H*-



OPC-21268 OPC-31260

Fig. 1

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1-benzozepine derivatives in our other investigation.[12] However, we found out that **1** were susceptible to isomerization under both acidic and basic conditions to give 4′-[5-(substituted methyl)-2,3-dihydro-1*H*-1-benzoazepine-1-carbonyl]-benzanilide derivatives (**2**) which did not fix the orientation of the substituent on the 5-position of benzoazepine, and **2** showed lower binding affinity potential for both V_{1A} and V_2 receptors compared with **1** (Fig. 2). On the basis of these results, we considered the cyclization of the 5-substituent, *i.e.*, the fusion to the 4,5-position of benzoazepine, in order to hold the orientation of the substituent on the 5-position of benzoazepine to the entgegen site (Fig. 2). Then, the 4′-(5,6-dihydro-4*H*-thiazolo[5,4-*d*][1]benzoazepine-6-carbonyl)benzanilide derivatives (thiazolobenzoazepine, **3**) and 4′-(1,4,5,6-tetrahydroimidazo[4,5-*d*][1]benzoazepine-6-carbonyl)benzanilide derivatives (imidazobenzoazepine, **4**) (Fig. 3) were investigated as a fusion of the azole ring to the 4,5-position of benzoazepine, because these compounds were able to be synthesized from our previously reported 4′-(5-oxo-2,3,4,5-tetrahydro-1*H*-1-benzoazepine-1-carbonyl)benzanilide derivatives.[11] In this report, we describe the synthesis and biological activity of these compounds.

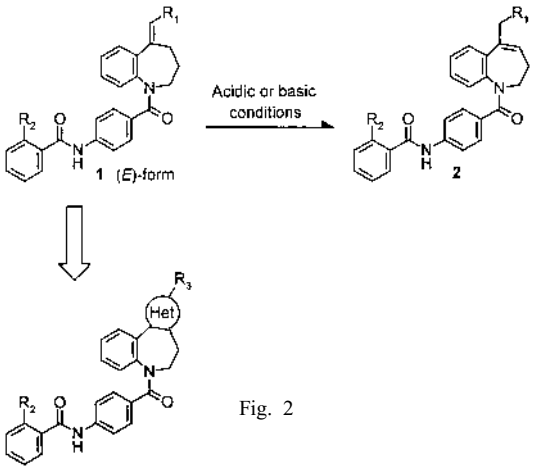


Fig. 2

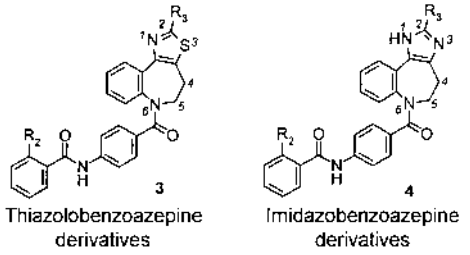


Fig. 3

Chemistry

The synthetic pathways for the preparation of the thiazolobenzoazepine and the imidazobenzoazepine derivatives listed in Tables 1—5 are shown in Charts 1—3.

The thiazolobenzoazepine derivatives were synthesized according to the route shown in Chart 1. The bromination of 4′-(5-oxo-2,3,4,5-tetrahydro-1*H*-1-benzoazepine-1-carbonyl)-2-phenylbenzanilide (**5**)[11] with bromine or $CuBr_2$ gave the key intermediate 4′-(4-bromo-5-oxo-2,3,4,5-tetrahydro-1*H*-1-benzoazepine-1-carbonyl)-2-phenylbenzanilide (**6**). Target thiazolobenzoazepine derivatives (**7**—**15**) were obtained by the condensation of **6** with the corresponding thioamide or thiourea.[13] 2-Aminoalkyl-substituted derivatives (**17a**—**c**) were prepared by the condensation of **6** with the corresponding phthalimidoalkyl-substituted thioamide,[13] followed by deprotection with methylamine.

The imidazobenzoazepine derivatives were synthesized according to the route shown in Chart 2. We attempted the condensation of **6** with the corresponding amidine[13]. In the case of the synthesis of the 2-methyl derivative, not only the imidazobenzoazepine derivative (**18**) but also the oxazolobenzoazepine derivative (**23**) were isolated. It was assumed that

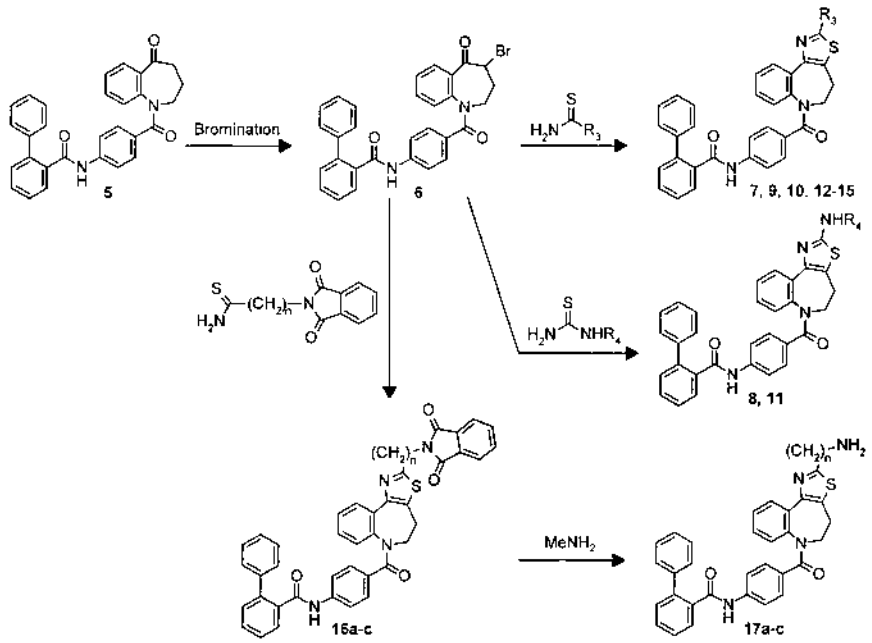


Chart 1

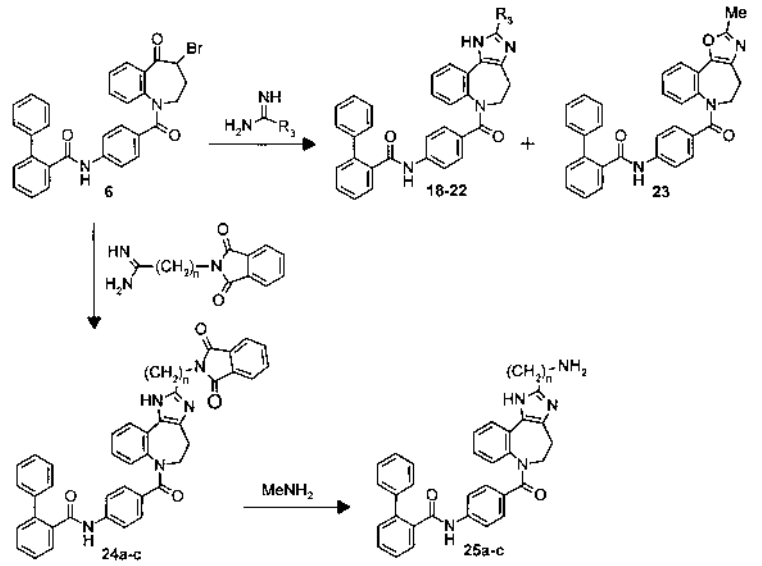


Chart 2

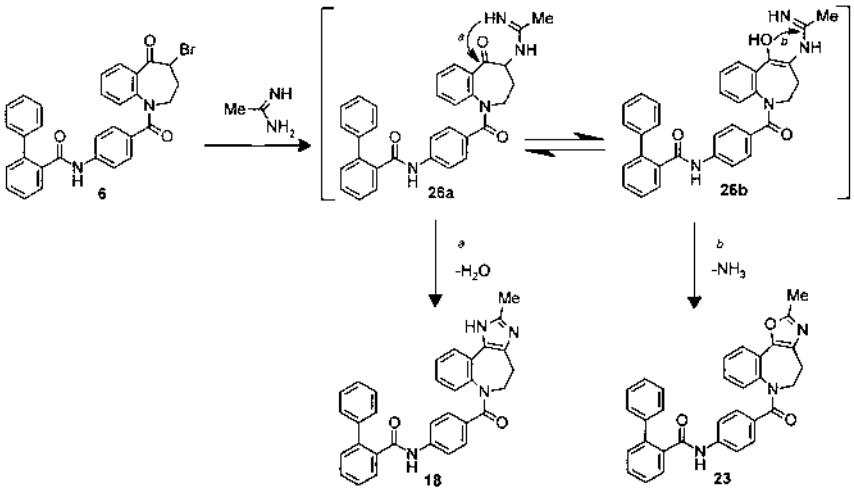


Fig. 4

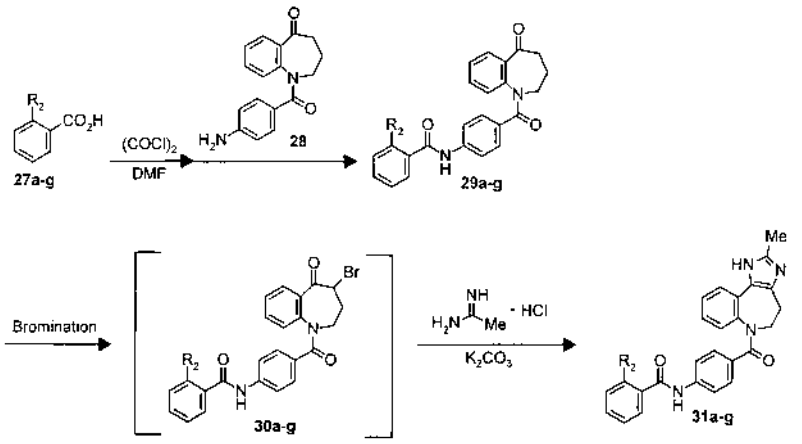
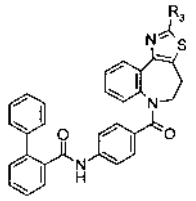
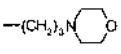
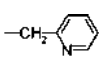
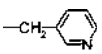
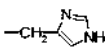
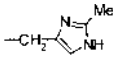


Chart 3

23 was produced by a nucleophilic attack of the 5-hydroxyl oxygen atom of the benzoazepine ring to the carbon atom of the amidine moiety during the intramolecular cyclization of enol intermediate (**26b**) (Fig. 4). On the other hand, in the case of the synthesis of other imidazobenzoazepine derivatives (**19**—**22**), since imidazobenzoazepine derivatives were produced as a major compound, minor oxazolobenzoazepine derivatives could not be isolated. 2-Aminoalkyl-substituted

Table 1. Receptor-Binding Affinities for 2-Substituted Thiazolobenzoazepine Derivatives



No.	R_3	Yield (%)[a]	mp (°C)	Formula[b]	^{1}H-NMR (DMSO-d_6) δ	MS m/z (M^++1)	Binding affinity (pK_i)		
							V_{1A}[c]	V_2[d]	OT[e]
7[f]	Me	33	165—168	$C_{32}H_{25}N_3O_2S \cdot 1/2H_2O$	2.75 (3H, s), 3.0—3.2 (2H, m), 3.5—3.6 (1H, m), 5.19 (1H, dd, J=4.4, 14 Hz), 6.65 (1H, d, J=7.8 Hz), 6.79 (1H, s), 6.85 (2H, d, J=8.8 Hz), 6.9—7.0 (3H, m), 7.2—7.6 (7H, m), 7.46 (1H, dt, J= 1.5, 7.8 Hz), 7.53 (1H, dt, J=1.5, 7.6 Hz), 7.86 (1H, d, J=7.3 Hz), 8.38 (1H, dd, J=1.0, 8.1 Hz)	516	7.87	7.89	6.83
8	$-NH_2$	83	>250	$C_{31}H_{24}N_4O_2S \cdot HBr$	2.9—3.3 (3H, m), 4.95 (1H, br), 6.82 (1H, d, J=7.3 Hz), 6.99 (2H, d, J=7.9 Hz), 7.15 (1H, t, J=7.6 Hz), 7.2—7.6 (12H, m), 7.85 (1H, d, J=7.8 Hz), 8.48 (2H, br), 10.31 (1H, s)	517	8.33	7.21	7.31
17a	$-CH_2NH_2$	40	175—180	$C_{32}H_{26}N_4O_2S \cdot HCl \cdot H_2O$[g]	3.08 (1H, br), 3.3—3.5 (2H, m), 4.47 (2H, br), 5.02 (1H, br), 6.81 (1H, d, J=7.3 Hz), 6.89 (2H, d, J=7.8 Hz), 7.11 (1H, t, J=7.3 Hz), 7.2—7.8 (12H, m), 7.90 (1H, br), 8.44 (1H, dd, J=1.5, 7.8Hz), 8.81 (2H, br), 10.35 (1H, s)	531	8.00	8.64	7.46
17b	$-(CH_2)_2NH_2$	23	187—192	$C_{33}H_{28}N_4O_2S \cdot HCl \cdot 2H_2O$	3.05 (1H, br), 3.2—3.4 (6H, m), 5.01 (1H, br), 6.78 (1H, d, J=7.8 Hz), 6.92 (2H, d, J=7.8 Hz), 7.09 (1H, t, J=7.3 Hz), 7.2—7.6 (12H, m), 8.14 (2H, br), 8.37 (1H, dd, J=1.5, 7.8 Hz), 10.33 (1H, s)	545	8.91	8.93	7.33
17c	$-(CH_2)_3NH_2$	32	185—188	$C_{34}H_{30}N_4O_2S \cdot HCl \cdot 2H_2O$[h]	2.09 (2H, q, J=7.5 Hz), 2.9—3.4 (7H, m), 5.01 (1H, d, J=10 Hz), 6.77 (1H, d, J=6.7 Hz), 6.90 (2H, d, J=7.3 Hz), 7.08 (1H, t, J=7.3 Hz), 7.2—7.6 (12H, m), 7.99 (2H, br), 8.33 (1H, d, J=7.9 Hz), 10.33 (1H, s)	559	8.40	8.96	7.16
9	$-(CH_2)_3NMe_2$	32	155—160	$C_{36}H_{34}N_4O_2S \cdot HCl \cdot 3/2H_2O$	2.19 (2H, br), 2.80 (6H, s), 3.0—3.4 (7H, m), 5.04 (1H, br), 6.78 (1H, d, J=7.3 Hz), 6.90 (2H, d, J=7.3 Hz), 7.08 (1H, t, J=7.1 Hz), 7.2—7.6 (12H, m), 8.34 (1H, dd, J=1.5, 8.3 Hz), 10.18 (1H, br), 10.33 (1H, s)	587	8.52	8.44	6.89
10		51	215—218	$C_{38}H_{36}N_4O_3S \cdot 2HCl \cdot 2H_2O$[i]	2.27 (2H, br), 3.0—3.5 (11H, m), 3.8—4.0 (4H, m), 5.00 (1H, br), 6.78 (1H, br), 6.91 (2H, d, J=7.3 Hz), 7.08 (1H, t, J=7.3 Hz), 7.2—7.6 (12H, m), 8.36 (1H, d, J=7.8 Hz), 10.34 (1H, s), 11.36 (1H, br)	629	7.92	7.41	7.82
11	$-NH(CH_2)_2NMe_2$	70	187—190	$C_{35}H_{33}N_5O_2S \cdot 2HCl \cdot 3H_2O$[j]	2.92 (6H, d, J=4.9 Hz), 2.9—3.2 (3H, m), 3.36 (2H, q, J=5.9 Hz), 3.71 (2H, br), 4.97 (1H, br), 6.72 (1H, d, J=7.3 Hz), 6.92 (2H, d, J=7.3 Hz), 7.02 (1H, t, J=7.1 Hz), 7.2—7.4 (7H, m), 7.46 (2H, dt, J=2.4, 7.8 Hz), 7.55 (2H, dd, J=7.3, 7.4 Hz), 7.84 (1H, br), 8.25 (1H, d, J=7.8 Hz), 9.88 (1H, br), 10.32 (1H, s)	514	8.76	8.59	7.38
12[f]		52	215—218	$C_{37}H_{28}N_4O_2S$	3.0—3.2 (2H, m), 3.5—3.7 (1H, m), 4.56 (2H, s), 5.18 (1H, d, J=13 Hz), 6.65 (1H, d, J=7.8 Hz), 6.79 (1H, br), 6.85 (2H, d, J=8.3 Hz), 6.9—7.0 (3H, m), 7.2—7.6 (11H, m), 7.70 (1H, dt, J=1.5, 7.6 Hz), 7.86 (1H, d, J=7.3Hz), 8.43 (1H, dd, J=1.5, 8.3 Hz), 8.64 (1H, d, J=3.9 Hz)	593	7.29	8.06	6.91
13		15	151—157	$C_{37}H_{28}N_4O_2S \cdot HCl \cdot 3/2H_2O$	3.03 (1H, br), 3.2—3.4 (2H, m), 4.66 (2H, s), 4.99 (1H, br), 6.78 (1H, br), 6.90 (2H, d, J=7.3 Hz), 7.08 (1H, t, J=7.6 Hz), 7.2—7.6 (12H, m), 8.03 (1H, dd, J=5.4, 8.3 Hz), 8.26 (1H, dd, J=1.5, 7.8 Hz), 8.61 (1H, d, J=8.3 Hz), 8.86 (1H, d, J=5.4 Hz), 9.04 (1H, s), 10.32 (1H, s)	593	7.74	8.25	6.97
14		38	192—195	$C_{35}H_{27}N_5O_2S \cdot 2HCl \cdot 3/2H_2O$	3.04 (1H, br), 3.2—3.4 (2H, m), 4.56 (2H, s), 5.00 (1H, br), 6.78 (1H, br), 6.90 (2H, d, J=7.3 Hz), 7.08 (1H, t, J=7.3 Hz), 7.2—7.6 (12H, m), 8.30 (1H, dd, J=1.0, 7.8 Hz), 9.14 (1H, s), 10.35 (1H, s), 14.6—14.8 (2H, m)	582	7.64	7.93	7.73
15		43	197—200	$C_{36}H_{29}N_5O_2S \cdot 2HCl \cdot H_2O$	2.58 (3H, s), 3.05 (1H, br), 3.2—3.4 (2H, br), 4.48 (2H, s), 5.00 (1H, br), 6.79 (1H, br), 6.90 (2H, d, J=7.3 Hz), 7.09 (1H, t, J=7.3 Hz), 7.2—7.6 (13H, m), 8.32 (1H, dd, J=1.5, 8.3 Hz), 10.34 (1H, s), 14.19 (1H, br), 14.40 (1H, br)	596	7.95	8.62	8.02

a) Yields were based on the final two steps (**8** and **17a**—**c**) and the final step (**7** and **9**—**15**) of the synthetic method and were not optimized. *b*) Analytical results were within±0.4% of the theoretical values unless otherwise noted. *c*) pK_i of [^{3}H]vasopressin binding to rat liver membranes. *d*) pK_i of [^{3}H]vasopressin binding to rabbit kidney membranes. *e*) pK_i of [^{3}H]oxytocin binding to rat uterus membranes. *f*) ^{1}H-NMR spectra was measured in $CDCl_3$. *g*) C (Calcd 65.69, Found 65.13), Cl (Calcd 6.06, Found 6.60). *h*) C (Calcd 64.70, Found 63.81). *i*) Cl (Calcd 9.61, Found 9.16). *j*) Cl (Calcd 9.92, Found 9.51).

derivatives (**25a**—**c**) were prepared by condensation of **6** with the corresponding phthalimidoalkyl-substituted amidine,[13] followed by deprotection with methylamine in the same manner as the synthesis of thiazolobenzoazepine derivatives.

2-Methylimidazobenzoazepine derivatives (**31a**—**g**), which had various substituents on the 2-position of the benzanilide moiety, were synthesized according to the route shown in Chart 3. The key intermediate benzoazepine-5-one derivatives (**29**) were obtained by the condensation of 1-(4-aminobenzoyl)-2,3,4,5-tetrahydro-1*H*-1-benzoazepin-5-one (**28**)[14] with the corresponding benzoic acid derivatives (**27**). After the bromination of **29** in the same manner as previously described, condensation with acetamidine gave target imidazobenzoazepine derivatives (**31a**—**g**).

Results and Discussion

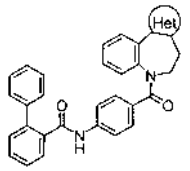
Binding Affinity Methods for determining the *in vitro* AVP and oxytocin (OT) receptor-binding affinity (rat liver for V_{1A}, rabbit kidney for V_2,[15] and rat uterus for OT) are described in a previous paper.[16] The results of the binding assay of compounds (**7**—**15**, **17**—**23**, **25**, and **31**) are shown in Tables 1—4.

2-Substituted thiazolobenzoazepine derivatives (**7**—**15** and **17**) were initially prepared as 4,5-heterocyclic ring-fused benzoazepine derivatives and tested (Table 1). The methyl derivative (**7**), which was prepared as an example of a simple substituent, showed similar binding affinity potentials for both V_{1A} and V_2 receptors, and that was satisfactory for our purpose. Therefore, we then attempted to introduce other substituents to the 2-position of the thiazolobenzoazepine ring.

From the results of our previous investigation of 2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine[16] and (*E*)-5-(substituted methylidene)-2,3,4,5-tetrahydro-1*H*-1-benzoazepine[11] derivatives, it was found that the introduction of a basic amino moiety to the substituent on the 5-position of the benzodiazepine and the benzoazepine ring was effective in increasing the binding affinity potentials for both V_{1A} and V_2 receptors. Then, the introduction of a substituent which contained a basic amino moiety to the 2-position of the thiazolobenzoazepine ring was investigated as a second modification. The 2-amino derivative (**8**) showed an increase in V_{1A} binding affinity and a decrease in V_2 binding affinity compared with **7**. However, aminoalkyl-substituted derivatives (**17a**—**c**) showed an increase in binding affinity for both V_{1A} and V_2 receptors. As an example, the aminoethyl derivative (**17b**) exhibited 50—60-fold more potent binding affinity compared with **7** for both V_{1A} and V_2 receptors, as well as similar affinity potentials for V_{1A} and V_2 receptors. From these results, the introduction of a basic aminoalkyl-substituent was found to enhance the binding affinity potentials in the case of thiazolobenzoazepine derivatives. The results of **17a**—**c** indicated that compounds which have an ethylene unit between the amino moiety and the thiazole ring showed the most potent binding affinity for both V_{1A} and V_2 receptors.

The 3-dimethylaminopropyl derivative (**9**) showed a decrease in V_2 receptor binding affinity, and the 3-morpholinopropyl derivative (**10**) showed a further decrease in both V_{1A} and V_2 receptor binding affinities compared with the aminopropyl derivative (**17c**). It seemed that increasing the bulkiness of the terminal amino moiety tended to decrease the binding affinity. The 2-dimethylaminoethylamino derivative (**11**), which converted the methylene unit adjacent to the thiazole ring of **9** to an amino unit, showed a slight increase in binding affinity for both V_{1A} and V_2 receptors compared with **9**. This was different from the results of the methyl (**7**) and amino (**8**) derivatives.

Table 2. Receptor-Binding Affinities for Azolobenzoazepine Derivatives



No.	Het	Binding affinity (pK_i)		
		V_{1A} [a]	V_2 [b]	OT [c]
7		7.87	7.89	6.83
18		9.05	8.83	7.56
23		8.37	8.58	7.28

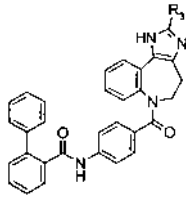
a—*c*) See footnotes in Table 1.

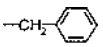
In our previous investigation, the introduction of a pyridylmethyl group to the substituent group on the 5-position of the benzoazepine and benzodiazepine ring was effective in increasing the binding affinity for both V_{1A} and V_2 receptors.[11,16] Therefore, pyridylmethyl (**12** and **13**) and imidazolylmethyl (**14** and **15**) derivatives were prepared; however, these compounds resulted in a decrease in binding affinity compared with aminoalkyl-substituted derivatives except for the V_2 binding affinity for **15**.

Next, the effect of modification of the azole ring for 4,5-heterocycle fused benzoazepine derivatives was investigated. The binding affinities for imidazobenzoazepine (**18**), oxazolobenzoazepine (**23**), and the thiazolobenzoazepine derivative (**7**) is shown in Table 2. As a result, the imidazobenzoazepine derivative (**18**) was found to exhibit the most potent binding affinity for both V_{1A} and V_2 receptors among these compounds, and their affinity potentials were almost similar to those of the aminoethyl-substituted thiazolobenzoazepine derivative (**17b**), despite the absence of an aminoalkyl-substituent. It was suggested that the basic azole ring was effective in increasing the binding affinity potentials for both V_{1A} and V_2 receptors.

Therefore, further modification of the substituent at the 2-position of the imidazobenzoazepine derivative was investigated. Alkyl (**19**—**22**) and aminoalkyl (**25a**—**c**) -substituted derivatives which were effective in the case of thiazolobenzoazepines (**17b** and **17c**) were prepared and tested (Table 3). In the case of the alkyl-substituted derivatives, the binding affinity potential decreased in the order of methyl (**18**) and ethyl (**19**)>cyclopropyl (**21**)>propyl (**20**)>benzyl (**22**). In particular, **22** showed a large decrease in binding affinity among these compounds. From the results of **22** and aryl-

Table 3. Receptor-Binding Affinities for 2-Substituted Imidazobenzoazepine Derivatives



No.	R_3	Yield (%)[a]	mp (°C)	Formula[b]	^{1}H-NMR (DMSO-d_6) δ	MS *m/z* (M^++1)	Binding affinity (pK_i)		
							V_{1A}[c]	V_2[d]	OT[e]
18	Me	38	>250	$C_{32}H_{26}N_4O_2$ ·HCl ·1/2H_2O	2.67 (3H, s), 2.98 (1H, t, *J*=12 Hz), 3.1—3.3 (2H, m), 4.99 (1H, d, *J*=11 Hz), 6.85 (1H, d, *J*=7.3 Hz), 6.93 (2H, d, *J*=7.3 Hz), 7.13 (1H, t, *J*=7.6 Hz), 7.2—7.6 (12H, m), 8.10 (1H, d, *J*=7.8 Hz), 10.31 (1H, s), 14.77 (2H, br)	499	9.05	8.83	7.56
19	Et	44	>250	$C_{33}H_{28}N_4O_2$ · HCl ·3/2H_2O[f]	1.39 (3H, t, *J*=7.8 Hz), 2.9—3.2 (5H, m), 4.99 (1H, d, *J*=11 Hz), 6.86 (1H, br), 6.94 (2H, d, *J*=7.8 Hz), 7.02 (1H, t, *J*=7.8 Hz), 7.2—7.6 (12H, m), 8.13 (1H, d, *J*=7.8 Hz), 10.32 (1H, s), 14.65 (1H, br), 14.81 (1H, br)	513	9.18	8.74	7.39
20	Pr	39	238—245	$C_{34}H_{30}N_4O_2$ ·HCl ·3/2H_2O	0.98 (3H, t, *J*=7.3 Hz), 1.85 (2H, q, *J*=7.5 Hz), 2.9—3.3 (5H, m), 5.00 (1H, d, *J*=13 Hz), 6.86 (1H, br), 6.93 (2H, d, *J*=7.8 Hz), 7.14 (1H, t, *J*=7.3 Hz), 7.2—7.6 (12H, m), 8.09 (1H, d, *J*=7.8 Hz), 10.32 (1H, s), 14.60 (1H, br), 14.72 (1H, br)	527	8.74	8.31	7.41
21		44	212—217	$C_{34}H_{28}N_4O_2$ ·HCl ·3/2H_2O	1.3—1.5 (4H, m), 2.9—3.3 (4H, m), 4.96 (1H, br), 6.83 (1H, d, *J*=7.3 Hz), 6.94 (2H, d, *J*=7.8 Hz), 7.12 (1H, t, *J*=7.3 Hz), 7.2—7.6 (12H, m), 8.18 (1H, d, *J*=7.8 Hz), 10.33 (1H, s), 14.51 (1H, br), 14.78 (1H, br)	525	8.91	8.52	7.69
22		34	210—213	$C_{38}H_{30}N_4O_2$ ·HCl ·3/2H_2O	2.9—3.2 (3H, m), 4.44 (2H, d, *J*=5.4 Hz), 4.96 (1H, br), 6.86 (1H, br), 6.93 (2H, d, *J*=7.8 Hz), 7.14 (1H, t, *J*=7.8 Hz), 7.2—7.6 (17H, m), 8.15 (1H, d, *J*=7.8 Hz), 10.32 (1H, s), 14.7—15.0 (2H, m)	575	8.11	8.07	6.39
25a	–$(CH_2)_2NH_2$	13	193—201	$C_{33}H_{29}N_5O_2$ ·2HCl ·4H_2O[g]	2.9—3.2 (3H, m), 3.42 (4H, br), 4.99 (1H, br), 6.8—7.1 (4H, m), 7.2—7.6 (12H, m), 8.15 (1H, d, *J*=7.9 Hz), 8.36 (2H, br), 10.29 (1H, s), 15.0 (1H, br)	528	9.47	9.08	7.17
25b	–$(CH_2)_3NH_2$	16	220—223	$C_{34}H_{31}N_5O_2$ ·2HCl ·4H_2O	2.15 (2H, t, *J*=7.6 Hz), 2.9—3.0 (3H, m), 3.1—3.3 (4H, m), 5.00 (1H, br), 6.8—7.1 (4H, m), 7.2—7.6 (12H, m), 8.1—8.2 (3H, m), 10.30 (1H, s), 14.8—15.0 (2H, m)	542	9.39	9.03	7.21
25c	–$(CH_2)_4NH_2$	16	191—197	$C_{35}H_{33}N_5O_2$ ·5/3HCl ·4H_2O[h]	1.65 (2H, t, *J*=7.5 Hz), 1.89 (2H, t, *J*=7.3 Hz), 2.8—3.2 (7H, m), 4.99 (1H, br), 6.8—7.1 (4H, m), 7.2—7.6 (12H, m), 7.9—8.0 (2H, m), 8.1—8.2 (1H, m), 10.30 (1H, s), 14.7—15.0 (2H, m)	556	9.29	9.30	7.54

a) Yields were based on the final two steps (**18** and **25a**—**c**) and the final step (**19**—**22**) of the synthetic method and were not optimized. *b*—*e*) See footnotes in Table 1. *f*) C (Calcd 68.80, Found 68.28). *g*) H (Calcd 5.84, Found 5.30), Cl (Calcd 10.54, Found 9.98). *h*) C (Calcd 61.06, Found 60.59), N (Calcd 10.17, Found 9.62).

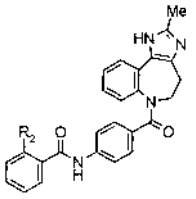
methyl-substituted thiazolobenzoazepine derivatives (**12**—**15**), increasing the bulkiness around the azole ring might result in a decrease in binding affinity.

Aminoalkyl-substituted derivatives (**25a**—**c**) exhibited an increase in binding affinity for both V_{1A} and V_2 receptors compared with alkyl-substituted derivatives, similar to the case of thiazolobenzoazepine derivatives. Therefore, it was found that the fusion of the basic imidazole ring on the 4,5-position of benzoazepine and the introduction of the aminoalkyl-substituent onto the 2-position of imidazobenzoazepine caused an additional enhancement of binding affinity for both V_{1A} and V_2 receptors. The binding affinity potential for the V_{1A} receptor was decreased in the order of **25a**>**25b**>**25c**, similar to alkyl-substituted derivatives (**18**—**22**); however, these relationships were not obvious for the V_2 receptor. From the comparison of **18**—**20** and **25a**—**c**, it seemed that increasing the hydrophilicity by introducing an amino moiety to the substituent was effective in increasing the binding affinity for both V_{1A} and V_2 receptors.

As another modification of **18**, conversion of the phenyl group at the 2-position of the benzanilide moiety was investigated (Table 4). Alkyl (**31a** and **31b**), alkoxy (**31c**—**e**), and fluoro (**31f**) -substituted derivatives showed a large decrease in binding affinity compared with **18**, except for the V_2 binding affinity for **31a**. On the other hand, the decrease in binding affinity of the 4-methylphenyl derivative (**31g**) was slight. Since **18** and **31g** had higher relative c log *P* values[17] compared with **31a**—**f**, it is assumed that increasing the lipophilicity by introduction of the phenyl ring on the 2-position of the benzanilide moiety was effective in increasing the binding affinity in the case of imidazobenzoazepine derivatives.

***In Vivo* Activity** The V_{1A} receptor antagonist activity was determined by measuring the inhibition of the AVP-in-

Table 4. Receptor-Binding Affinities for 2-Methylimidazobenzoazepine Derivatives



No.	R_2	Yield (%)[a]	mp (°C)	Formula[b]	^{1}H-NMR (DMSO-d_6) δ	MS *m/z* (M^++1)	Binding affinity (pK_i) V_{1A}[c]	V_2[d]	OT[e]
18	Ph						9.05	8.83	7.56
31a	Me	29	239 (dec.)	$C_{27}H_{24}N_4O_2 \cdot HCl \cdot H_2O$	2.33 (3H, s), 2.70 (3H, s), 3.00 (1H, t, *J*=12 Hz), 3.1—3.3 (2H, m), 5.01 (1H, d, *J*=11 Hz), 6.88 (1H, d, *J*=7.3 Hz), 7.01 (2H, d, *J*=7.8 Hz), 7.14 (1H, t, *J*=7.6 Hz), 7.2—7.5 (5H, m), 7.56 (2H, d, *J*=7.8 Hz), 8.17 (1H, d, *J*=7.3 Hz), 10.40 (1H, s), 14.91 (2H, br)	437	7.77	8.55	7.17
31b	isoPr	19	151—153	$C_{29}H2_8N_4O_2 \cdot HCl \cdot H_2O$[f]	1.78 (6H, t, *J*=6.8 Hz), 2.69 (3H, s), 3.00 (1H, t, *J*=12 Hz), 3.1—3.3 (3H, m), 5.01 (1H, d, *J*=10 Hz), 6.93 (1H, d, *J*=7.3 Hz), 7.00 (2H, d, *J*=7.8 Hz), 7.2—7.4 (5H, m), 7.56 (2H, d, *J*=8.3 Hz), 8.11 (1H, d, *J*=7.8 Hz), 10.46 (1H, s), 14.77 (2H, br)	465	7.85	7.42	6.99
31c	OMe	15	228—235	$C_{27}H_{24}N_4O_3 \cdot HCl \cdot 1/2H_2O$	2.69 (3H, s), 3.00 (1H, t, *J*=12 Hz), 3.1—3.3 (2H, m), 3.85 (3H, s), 5.01 (1H, d, *J*=10 Hz), 6.88 (1H, d, *J*=7.3 Hz), 6.9—7.1 (4H, m), 7.15 (2H, d, *J*=8.3 Hz), 7.36 (1H, t, *J*=7.6 Hz), 7.48 (1H, t, *J*=7.8 Hz), 7.55 (2H, t, *J*=5.9 Hz), 8.14 (1H, d, *J*=7.8 Hz), 10.20 (1H, s), 14.83 (2H, br)	453	7.98	7.45	6.47
31d	OEt	37	221—225	$C_{28}H_{26}N_4O_3 \cdot HCl \cdot H_2O$	1.34 (3H t, *J*=6.7 Hz), 2.70 (3H, s), 3.00 (1H, t, *J*=12 Hz), 3.1—3.3 (2H, m), 4.14 (2H, q, *J*=6.7 Hz), 5.16 (1H, d, *J*=10 Hz), 6.88 (1H, d, *J*=6.7 Hz), 7.0—7.1 (3H, m), 7.14 (2H, d, *J*=8.6 Hz), 7.35 (1H, t, *J*=7.3 Hz), 7.48 (1H, t, *J*=7.0 Hz), 7.54 (2H, d, *J*=7.9 Hz), 7.63 (1H, d, *J*=6.7 Hz), 8.18 (1H, d, *J*=7.3 Hz), 10.19 (1H, s), 14.86 (2H, br)	467	7.93	7.63	6.65
31e	O-isoPr	55	>250	$C_{29}H_{28}N_4O_3 \cdot HCl \cdot 2H_2O$	1.30 (6H, d, *J*=5.9 Hz), 2.69 (3H, s), 3.01 (1H, t, *J*=13 Hz), 3.1—3.3 (2H, m), 4.72 (1H, q, *J*=6.0 Hz), 5.00 (1H, br), 6.95 (1H, d, *J*=7.8 Hz), 7.0—7.2 (5H, m), 7.37 (1H, t, *J*=7.8 Hz), 7.4—7.5 (3H, m), 7.65 (1H, d, *J*=7.8 Hz), 8.10 (1H, d, *J*=7.8 Hz), 10.18 (1H, s), 14.74 (2H, br)	481	8.21	7.23	6.58
31f	F	82	>250	$C_{26}H_{21}FN_4O_2 \cdot HCl \cdot 1/2H_2O$	2.70 (3H, s), 3.01 (1H, t, *J*=12 Hz), 3.1—3.2 (2H, m), 5.02 (1H, d, *J*=11 Hz), 6.87 (1H, d, *J*=7.3 Hz), 7.02 (2H, d, *J*=7.8 Hz), 7.14 (1H, t, *J*=7.6 Hz), 7.2—7.6 (6H, m), 7.63 (1H, t, *J*=6.8 Hz), 8.18 (1H, d, *J*=7.8 Hz), 10.55 (1H, s), 14.9 (2H, br)	440	7.71	7.51	6.24
31g	4-MePh	20	220—223	$C_{33}H_{28}N_4O_2 \cdot HCl \cdot H_2O$	2.27 (3H, s), 2.67 (3H, s), 2.99 (1H, t, *J*=12 Hz), 3.1—3.3 (2H, m), 4.99 (1H, d, *J*=11 Hz), 6.87 (1H, d, *J*=7.3 Hz), 6.94 (2H, d, *J*=8.3 Hz), 7.0—7.7 (12H, m), 8.09 (1H, d, *J*=7.8 Hz), 10.33 (1H, s), 14.58 (1H, br), 14.74 (1H, br)	513	8.60	8.63	7.23

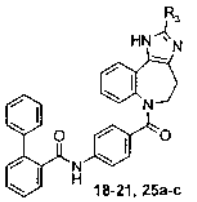
a) Yields were based on the final two steps of the synthetic method and were not optimized. *b*—*e*) See footnotes in Table 1. *f*) C (Calcd 67.11, Found 67.67).

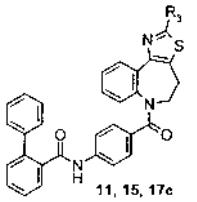
duced diastolic blood pressure (DBP) response in pithed rats after intravenous (i.v.) administration. We determined the dose of the compounds causing a 50% inhibition (ID_{50}) of the pressor response to AVP. The V_2 receptor antagonist activity was determined by measuring the effect on the urine volume in dehydrated conscious rats after i.v. administration. We determined the dose (ED_3) which caused an increase in urine volume by 3 ml during 2 h after administering the compound. Oral activity was determined by measuring the effect on urine volume in dehydrated conscious rats for the V_2 receptor. Details of the experimental methods were described in a previous paper.[16]

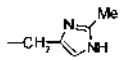
Compounds (**18**—**21** and **25a**—**c**), which showed potent binding affinities, were selected among the imidazobenzoazepine derivatives and tested for oral activity (Table 5). 2-Alkyl-substituted derivatives (**18**—**21**) showed a significant increase in urine volume (>6 ml) for 2 h at 3 mg/kg drug administration. Especially, the methyl derivative (**18**) exhibited the most potent activity (13.27±0.36 ml). On the other hand, 2-aminoalkyl-substituted derivatives (**25a**—**c**) showed poor urine volume compared with 2-alkyl-substituted derivatives (**18**—**21**) despite their high binding affinity potentials. From these results, it is assumed that increasing the hydrophilicity by the introduction of the aminoalkyl group tended to decrease the oral availability.

Among thiazolobenzoazepine derivatives, **11** (aminoalky-

Table 5. Oral Activity and AVP-Antagonist Activities for 2-Substituted Imidazobenzoazepine and Thiazolobenzoazepine Derivatives

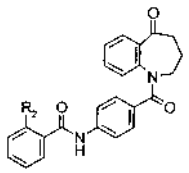




No.	R_3	Binding affinity (pK_i)		Oral activity	Antagonist activity	
		V_{1A}	V_2	UV (ml)[a]	V_{1A} ID_{50} (mg/kg)[b]	V_2 ED_3 (mg/kg)[c]
18	Me	9.05	8.83	13.27±0.36	0.013	0.028
19	Et	9.18	8.74	6.50±0.35	0.012	0.065
20	Pr	8.74	8.31	7.09±1.60	0.0070	0.063
21		8.91	8.52	10.14±0.50	0.0072	0.054
25a	$-(CH_2)_2NH_2$	9.47	9.08	1.57±0.65	NT[d]	NT
25b	$-(CH_2)_3NH_2$	9.39	9.03	1.30±0.42	NT	NT
25c	$-(CH_2)_4NH_2$	9.29	9.30	3.15±0.82	NT	NT
11	$-NH(CH_2)_2NMe_2$	8.76	8.59	4. 00±0.23 (10 mg/kg)	0.047	0.71
15		7.95	8.62	2. 06±0.53 (10 mg/kg)	0.17	0.51
17c	$-(CH_2)_3NH_2$	8.40	8.96	1. 80±0.54 (10 mg/kg)	0.11	0.50

a) UV values mean urine volume (ml) during 2 h after oral administration of the drug (3 mg/kg unless otherwise noted) to rats and are expressed as mean±S.E.M. *b*) ID_{50} represents the drug concentration (mg/kg) required to inhibit the AVP-induced pressor response in pithed rats by 50% by intravenous administration. *c*) 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. *d*) NT: not tested.

Table 6. Physical and Spectral Data of 5-Oxobenzoazepine Derivatives[a]



No.	R_2	Yield (%)[b]	mp (°C)	Formula[c]	^{1}H-NMR ($CDCl_3$) δ	MS *m/z* (M^++1)
29b	isoPr	89	172—174	$C_{27}H_{26}N_2O_3$	1.23 (6H, d, *J*=6.9 Hz), 2.0—2.3 (2H, br), 2.89 (2H, t, *J*=5.8 Hz), 3.3—3.4 (1H, m), 6.77 (1H, d, *J*=8.3 Hz), 7.2—7.5 (10H, m), 7.57 (1H, s), 7.88 (1H, m)	427
29c	OMe	91	166—169	$C_{25}H_{22}N_2O_4$	2.0—2.3 (2H, br), 2.91 (2H, t, *J*=6.3 Hz), 4.03 (3H, s), 6.76. (1H, d, *J*=7.4 Hz), 7.02 (1H, d, *J*=8.3 Hz), 7.12 (1H, dt, *J*=1.0, 7.3 Hz), 7.3—7.4 (4H, m), 7.5—7.6 (3H, m), 7.87 (1H, dd, *J*=1.5, 7.9 Hz), 8.24 (1H, dd, *J*=1.5, 7.9 Hz), 9.86 (1H, s)	415
29d	OEt	91	175—176	$C_{26}H_{24}N_2O_4$	1.60 (3H, t, *J*=6.8 Hz), 2.0—2.3 (2H, br), 2.91 (2H, t, *J*=6.4 Hz), 4.26 (2H, q, *J*=6.8 Hz), 6.76 (1H, d, *J*=6.8 Hz), 6.99 (1H, d, *J*=8.3 Hz), 7.10 (1H, dt, *J*=1.0, 7.4 Hz), 7.2—7.3 (4H, m), 7.4—7.6 (3H, m), 7.88 (1H, dd, *J*=2.4, 7.3 Hz), 8.26 (1H, dd, *J*=1.9, 7.8 Hz), 10.19 (1H, s)	429
29e	O-isoPr	37	181—183	$C_{27}H_{26}N_2O_4$	1.49 (6H, d, *J*=5.9 Hz), 2.0—2.3 (2H, br), 2.91 (2H, t, *J*=6.4 Hz), 4.8—4.9 (1H, m), 6.76 (1H, d, *J*=8.8 Hz), 7.06 (1H, d, *J*=8.3 Hz), 7.10 (1H, dt, *J*=1.0, 7.8 Hz), 7.2—7.3 (4H, m), 7.4—7.6 (3H, m), 7.88 (1H, dd, *J*=1.9, 7.4 Hz), 8.26 (1H, dd, *J*=1.9, 7.8 Hz), 10.28 (1H, s)	443
29f	F	97	232—235	$C_{24}H_{19}FN_2O_3 \cdot 1/5H_2O$	2.0—2.3 (2H, br), 2.91 (2H, t, *J*=6.4 Hz), 6.75 (1H, d, *J*=7.8 Hz), 7.1—7.4 (6H, m), 7.5—7.6 (3H, m), 7.88 (1H, dd, *J*=1.9, 7.3 Hz), 8.13 (1H, dt, *J*=1.9, 7.5 Hz), 8.46 (1H, d, *J*=16 Hz)	403

a) Data of **29a** (R_2=Me) and **29g** (R_2=4-MePh) were shown in reference (11). *b*) Yields were based on the final step of the synthetic method and were not optimized. c) See footnote in Table 1.

lamino), **15** (arylmethyl), and **17c** (aminoalkyl) were selected and tested for oral activity. These compounds showed poor urine volume despite the 10 mg/kg drug administration. However, the relative c log *P* values[17] of the tested compounds, **18**<**17c**<**19**<**15**<**11**<**20**, showed that the relationship between hydrophilicity and oral activity for the thiazolobenzoazepine derivatives was not obvious.

Therefore, we examined antagonist activities following the i.v. administration of these compounds and compared imidazobenzoazepine with thiazolobenzoazepine derivatives (Table 5). Imidazobenzoazepine derivatives (**18**—**21**) showed 0.007—0.013 mg/kg as the IC_{50} value for the V_{1A} receptor, and 0.028—0.065 mg/kg as the ED_3 value for the V_2 receptor. On the other hand, thiazolobenzoazepine derivatives (**11**, **15**, and **17c**) showed 0.047—0.11 mg/kg as the IC_{50} value for the V_{1A} receptor, and 0.50—0.71 mg/kg as the ED_3 value for the V_2 receptor. From these results, thiazolobenzoazepine derivatives were found to show low antagonist activities despite their high binding activity potentials. Therefore, it was suggested that imidazobenzoazepine derivatives were more favorable for exhibiting high activity potentials *in vivo*.

In summary, the 2-methylimidazobenzoazepine derivative (**18**) exhibited both potent antagonistic activities and the most potent oral activity. Since we are searching for an orally active AVP antagonist, compound **18** is the most favorable for our purpose.

Conclusions

In this report, 4′-(1,4,5,6-tetrahydroimidazo[4,5-*d*][1]benzoazepine-6-carbonyl)benzanilide derivatives and 4′-(5,6-dihydro-4*H*-thiazolo[5,4-*d*][1]benzoazepine-6-carbonyl)benzanilide derivatives were synthesized in order to develop an orally active AVP antagonist for both V_{1A} and V_2 receptors, and their pharmacological properties were evaluated. As a result, the fusion of the imidazole ring to the 4,5-position of benzoazepine (imidazo[4,5-*d*][1]benzoazepine moiety) and the introduction of an aminoalkyl group to the 2-position of imidazobenzoazepine and thiazolobenzoazepine moiety were found to enhance the binding affinity potentials. In addition, 2-alkyl-substituted imidazobenzoazepine derivatives showed potent *in vivo* activities. Especially, 4′-(2-methyl-1,4,5,6-tetrahydroimidazo[4,5-*d*][1]benzoazepine-6-carbonyl)-2-phenylbenzanilide monohydrochloride (**18**, YM087=conivaptan hydrochloride) exhibited potent binding affinity, antagonist activity, and oral availability. Further investigation of the pharmacological profile of YM087 was reported.[3,10,18,19] YM087 should therefore prove to be a novel and valuable compound for investigating the physiological and pathophysiological roles of AVP; it may be a valuable therapeutic agent in the treatment of chronic disorders such as CHF, edema, hyponatremia, and the syndrome of inappropriate AVP secretion. YM087 is currently under clinical trial for the treatment of 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. All organic extracts were dried over anhydrous $MgSO_4$. Chromatographic purification was performed on Merck KGaA Silica-gel 60 (0.040—0.063 mm).

Thioamide, thiourea, and amidine were commercially available or synthesized according to the literature.[13]

4′-(4-Bromo-5-oxo-2,3,4,5-tertrahydro-1*H*-1-benzoazepine-1-carbonyl)-2-phenylbenzanilide (6) Bromine (800 mg) was slowly added to a solution of 4′-(5-oxo-2,3,4,5-tertrahydro-1*H*-1-benzoazepine-1-carbonyl)-2-phenylbenzanilide (**5**)[11] (2.0 g) in acetic acid (AcOH) (28 ml). To the mixture was added 25% HBr in AcOH (2 ml) and the whole was stirred for 60 min at room temperature. It was poured into water, and the resulting precipitate was filtered and washed with water to give **6** (2.2 g, 94%) as a colorless powder, mp 124—128 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.44 (1H, br), 2.69 (1H, br), 4.9—5.0 (1H, m), 6.69 (1H, d, J=7.8 Hz), 6.84 (1H, s), 6.92 (2H, d, J=8.4 Hz), 7.19 (2H, d, J=8.4 Hz), 7.2—7.6 (10H, m), 7.77 (1H, dd, J=1.6, 7.8 Hz), 7.87 (1H, d, J=7.6 Hz). FAB-MS *m/z*: 539, 541 (M^++1). *Anal.* Calcd for $C_{30}H_{23}BrN_2O_3 \cdot 2/3H_2O$: C, 65.34; H, 4.45; Br, 14.49; N,5.08. Found: C, 65.29; H, 4.18; Br, 14.48; N,5.06.

4′-(5,6-Dihydro-2-methyl-4*H*-thiazolo[5,4-*d*][1]benzoazepine-6-carbonyl)-2-phenylbenzanilide (7) Thioacetamide (110 mg) was added to a solution of **6** (540 mg) in 2-propanol (20 ml), and the mixture was stirred for 8 h at reflux temperature. It was cooled and concentrated. The residue was chromatographed over silica gel using 1 : 5 ethyl acetate (AcOEt)–hexane and crystallized from diethylether to give **7** (170 mg, 33%) as a colorless powder, mp 165—168 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.75 (3H, s), 3.0—3.2 (2H, m), 3.5—3.6 (1H, m), 5.1—5.2 (1H, m), 6.65 (1H, d, J=7.8 Hz), 6.79 (1H, s), 6.85 (2H, d, J=8.8 Hz), 6.9—7.0 (3H, m), 7.2—7.6 (9H, m), 7.86 (1H, d, J=7.3 Hz), 8.38 (1H, dd, J=1.0, 8.1 Hz). FAB-MS *m/z*: 516 (M^++1). *Anal.* Calcd for $C_{32}H_{25}N_3O_2S \cdot 1/2H_2O$: C, 73.26; H, 4.99; N, 8.01; S, 6.11. Found: C, 73.58; H, 4.83; N, 8.02; S, 6.04.

Compounds **9**—**15** were synthesized in the same manner.

4′-(2-Amino-5,6-dihydro-4*H*-thiazolo[5,4-*d*][1]benzoazepine-6-carbonyl)-2-phenylbenzanilide Monohydrobromide (8) $CuBr_2$ (560 mg) was added to a solution of **5** (500 mg) in $CHCl_3$ (15 ml) and AcOEt (1.5 ml), and the mixture was stirred vigorously for 3 h at reflux temperature. It was then cooled to room temperature, and insoluble material was removed by filtration. The filtrate was washed with saturated aqueous $NaHCO_3$ and brine, dried, and concentrated. The residue was dissolved in ethanol (EtOH) (12 ml), and to the solution was added thiourea (100 mg). The whole was stirred for 3 h at reflux temperature. It was cooled and the resulting precipitate was filtrated and washed with EtOH to give **8** (540 mg, 83%) as a colorless powder, mp >250 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.9—3.3 (3H, m), 4.95 (1H, br), 6.82 (1H, d, J=7.3 Hz), 6.99 (2H, d, J=7.9 Hz), 7.15 (1H, t, J=7.6 Hz), 7.2—7.6 (12H, m), 7.85 (1H, d, J=7.8 Hz), 8.48 (2H, br), 10.31 (1H, s). FAB-MS *m/z*: 517 (M^++1). *Anal.* Calcd for $C_{31}H_{24}N_4O_2S \cdot HBr$: C, 62.31; H, 4.22; Br, 13.37; N, 9.38; S, 5.37. Found: C, 62.39; H, 4.42; Br, 13.51; N, 9.18; S, 5.21.

4′-(2-Aminomethyl-5,6-dihydro-4*H*-thiazolo[5,4-*d*][1]benzoazepine-6-carbonyl)-2-phenylbenzanilide Monohydrochloride (17a) (Phthalimido-2-yl)thioacetamide (150 mg) was added to a solution of **6** (370 mg) in 2-propanol (20 ml), and the mixture was stirred for 10 h at reflux temperature. It was cooled and the resulting precipitate was filtrated and washed with 2-propanol to give crude 4′-[5,6-dihydro-2-(phthalimido-2-yl)methyl-4*H*-thiazolo[5,4-*d*][1]benzoazepine-6-carbonyl]-2-phenylbenzanilide (**16a**) (240 mg, 53%) as a colorless powder. A 40% solution of methylamine in methanol (MeOH) (1.7 ml) was added to a suspension of **16a** (220 mg) in MeOH (10 ml), and the mixture was stirred for 6 h at room temperature. It was concentrated and the residue was dissolved in $CHCl_3$. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried, and concentrated. The residue was chromatographed over silica gel using 20 : 1 $CHCl_3$–MeOH. The resulting material was dissolved in MeOH (10 ml). A 4 N solution of HCl in AcOEt (0.5 ml) was added to the solution and then concentrated. The residue was crystallized from acetonitrile (MeCN) to give **17a** (140 mg, 40%) as a pale yellow powder, mp 175—180 °C. ^{1}H-NMR (DMSO-d_6) δ: 3.08 (1H, br), 3.3—3.5 (2H, m), 4.47 (2H, br), 5.02 (1H, br), 6.81 (1H, d, J=7.3 Hz), 6.89 (2H, d, J=7.8 Hz), 7.11 (1H, t, J=7.3 Hz), 7.2—7.8 (12H, m), 7.90 (1H, br), 8.44 (1H, dd, J=1.5, 7.8 Hz), 8.81 (2H, br), 10.35 (1H, s). FAB-MS *m/z*: 531 (M^++1). *Anal.* Calcd for $C_{32}H_{26}N_4O_2S \cdot HCl \cdot H_2O$: C, 65.69; H, 5.00; Cl, 6.06; N, 9.58; S, 5.48. Found: C, 65.13; H, 5.21; Cl, 6.60; N, 9.60; S, 5.25.

Compounds **17b** and **17c** were synthesized in the same manner.

4′-(2-Methyl-1,4,5,6-tetrahydroimidazo[4,5-*d*][1]benzoazepine-6-carbonyl)-2-phenylbenzanilide Monohydrochloride (18) and 4′-(2-Methyl-5,6-dihydro-4*H*-oxazolo[4,5-*d*][1]benzoazepine-6-carbonyl)-2-phenylbenzanilide (23) $CuBr_2$ (560 mg) was added to a solution of **5** (500 mg) in $CHCl_3$ (15 ml) and AcOEt (1.5 ml), and the mixture was stirred vigorously for 3 h at reflux temperature. It was cooled to room temperature, and insolu-

ble material was removed by filtration. The resulting solution was washed with saturated aqueous $NaHCO_3$ and brine, dried, and concentrated. The residue was dissolved in MeCN (10 ml), and to the solution was added acetamidine hydrochloride (510 mg) and K_2CO_3 (750 mg). The whole was stirred vigorously for 1.5 h at reflux temperature. It was cooled to room temperature, and insoluble material was removed by filtration. The resulting solution was concentrated and the residue was dissolved in $CHCl_3$. The whole was washed with water and brine, dried, and concentrated. The residue was chromatographed over silica gel using 20 : 1 $CHCl_3$–MeOH and recrystallized from AcOEt to give **23** (40 mg, 7.4%) and a free amine of **18** (290 mg, 53%). The free amine of **18** (290 mg) was dissolved in EtOH (5 ml), and to the solution was added a 4 N solution of HCl in AcOEt (0.2 ml) at 0—5 °C. The resulting precipitate was filtered and washed with EtOH to give **18** (220 mg, 38%).

18: Colorless powder, mp >250 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.67 (3H, s), 2.98 (1H, t, J=12 Hz), 3.1—3.3 (2H, m), 4.99 (1H, d, J=11 Hz), 6.85 (1H, d, J=7.3 Hz), 6.93 (2H, d, J=7.3 Hz), 7.13 (1H, t, J=7.6 Hz), 7.2—7.6 (12H, m), 8.10 (1H, d, J=7.8 Hz), 10.31 (1H, s), 14.77 (2H, br). FAB-MS m/z: 499 (M^++1). *Anal.* Calcd for $C_{32}H_{26}N_4O_2 \cdot HCl \cdot 1/2H_2O$: C,70.65; H, 5.18; Cl; 6.52; N, 10.30. Found: C, 70.67; H, 5.29; Cl, 6.41; N, 10.13.

23: Colorless powder, mp 234—236 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.57 (3H, s), 2.8—3.0 (2H, m), 3.29 (1H, t, J=13 Hz), 5.17 (1H, d, J=14 Hz), 6.66 (1H, d, J=7.8 Hz), 6.8—7.0 (6H, m), 7.22 (1H, dt, J=1.0, 7.8 Hz), 7.3—7.5 (6H, m), 7.53 (1H, dt, J=1.5, 7.3 Hz), 7.7 (1H, dt, J=1.5, 7.8 Hz), 7.84 (1H, d, J=7.3 Hz). FAB-MS m/z: 500 (M^++1). *Anal.* Calcd for $C_{32}H_{25}N_4O_3$: C, 76.94; H, 5.04; N, 8.41. Found: C, 76.49; H, 5.01; N, 8.11.

4′-(2-Ethyl-1,4,5,6-tetrahydroimidazo[4,5-*d*][1]benzoazepine-6-carbonyl)-2-phenylbenzanilide Monohydrochloride (19) Propionamidine hydrochloride (370 mg) and K_2CO_3 (1.1 g) were added to a solution of **6** (550 mg) in MeCN (20 ml), and the mixture was stirred for 1 h at reflux temperature. It was cooled to room temperature, and insoluble material was removed by filtration. The resulting solution was concentrated and the residue was dissolved in $CHCl_3$. The solution was washed with saturated aqueous $NaHCO_3$ and brine, dried, and concentrated. The residue was chromatographed over silica gel using 20 : 1 $CHCl_3$–MeOH to give a free amine of **19** (350 mg, 66%). The free amine of **19** (350 mg) was dissolved in a 4 N solution of HCl in AcOEt (5 ml), and the mixture was stirred at 0—5 °C. A resulting precipitate was recrystallized from AcOEt to give **19** (250 mg, 44%) as a colorless powder, mp >250 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.39 (3H, t, J=7.8 Hz), 2.9—3.2 (5H, m), 4.99 (1H, d, J=11 Hz), 6.86 (1H, br), 6.94 (2H, d, J=7.8 Hz), 7.02 (1H, t, J=7.8 Hz), 7.2—7.6 (12H, m), 8.13 (1H, d, J=7.8 Hz), 10.32 (1H, s), 14.65 (1H, br), 14.81 (1H, br). FAB-MS m/z: 513 (M^++1). *Anal.* Calcd for $C_{33}H_{28}N_4O_2 \cdot HCl \cdot 3/2H_2O$: C, 68.80; H, 5.60; Cl, 6.15; N, 9.73. Found: C, 68.28; H, 5.54; Cl, 6.48; N, 9.62.

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

4′-(2-Aminoethyl-1,4,5,6-tetrahydroimidazo[4,5-*d*][1]benzoazepine-6-carbonyl)-2-phenylbenzanilide Dihydrochloride (25a) (Phthalimido-2-yl)propionamidine hydrochloride (4.2 g) and K_2CO_3 (3.1 g) were added to a solution of **6** (500 mg) in $CHCl_3$ (150 ml), and the mixture was stirred for 18 h at reflux temperature. It was cooled and washed with saturated aqueous $NaHCO_3$ and brine, dried, and concentrated. The residue was chromatographed over silica gel using 50 : 1 $CHCl_3$–MeOH to give crude 4′-[2-(phthalimido-2-yl)ethyl-1,4,5,6-tetrahydroimidazo[4,5-*d*][1]benzoazepine-6-carbonyl]-2-phenylbenzanilide (**24a**) (390 mg, 64%). A 40% solution of methylamine in MeOH (10 ml) was added to a solution of **24a** (220 mg) in MeOH (10 ml), and the mixture was stirred for 4.5 h at room temperature. It was then concentrated and the residue was dissolved in $CHCl_3$. The organic layer was extracted with 1 N HCl. The aqueous layer was made basic with 1 N NaOH, and extracted with $CHCl_3$. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried, and concentrated. The residue was dissolved in AcOEt. A 4 N solution of HCl in AcOEt solution (0.5 ml) was added to the solution and then concentrated. The residue was crystallized from AcOEt–EtOH to give **25a** (70 mg, 13%) as a colorless powder, mp 193—201 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.9—3.2 (3H, m), 3.42 (4H, br), 4.99 (1H, br), 6.8—7.1 (4H, m), 7.2—7.6 (12H, m), 8.15 (1H, d, J=7.9 Hz), 8.36 (2H, br), 10.29 (1H, s), 15.0 (1H, br). FAB-MS m/z: 528 (M^++1). *Anal.* Calcd for $C_{33}H_{29}N_5O_2 \cdot 2HCl \cdot 4H_2O$: C, 58.93; H, 5.84; Cl, 10.54; N, 10.41. Found: C, 59.31; H, 5.30; Cl, 9.98; N, 10.37.

Compounds **25b** and **25c** were synthesized in the same manner.

2-Isopropyl-4′-(5-oxo-2,3,4,5-tetrahydro-1*H*-1-benzoazepine-1-carbonyl)benzanilide (29b) To an ice-cooled solution of 2-isopropylbenzoic acid (**27b**) (1.0 g) in CH_2Cl_2 (14 ml) were added a catalytic amount of *N*,*N*-dimethylformamide and oxalyl chloride (1.2 g), and the mixture was stirred for 1 h. It was concentrated and the residue was dissolved in CH_2Cl_2 (14 ml). This solution was added dropwise to an ice-cooled solution of 1-(4-aminobenzoyl)-2,3,4,5-tetrahydro-1*H*-1-benzoazepin-5-one (**28**)[14] (1.7 g) and Et_3N (920 mg) in CH_2Cl_2 (34 ml), and the mixture was stirred for 2 h at room temperature. The mixture was washed with saturated aqueous $NaHCO_3$ and brine, dried, and concentrated. The residue was collected by filtration to give **29b** (2.3 g, 89%) as a colorless powder, mp 172—174 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (6H, d, J=6.9 Hz), 2.0—2.3 (2H, br), 2.89 (2H, t, J=5.8 Hz), 3.3—3.4 (1H, m), 6.77 (1H, d, J=8.3 Hz), 7.2—7.5 (10H, m), 7.57 (1H, s), 7.88 (1H, m). FAB-MS m/z: 427 (M^++1). *Anal.* Calcd for $C_{27}H_{26}N_2O_3$: C, 73.29; H, 5.92; N, 6.33. Found: C, 73.44; H, 5.95; N, 6.28.

Compounds **29c**—**f** were synthesized in the same manner.

2-Methyl-4′-(2-methyl-1,4,5,6-tetrahydroimidazo[4,5-*d*][1]benzoazepine-6-carbonyl)benzanilide Monohydrochloride (31a) $CuBr_2$ (2.5 g) was added to a solution of 2-methyl-4′-(5-oxo-2,3,4,5-tetrahydro-1*H*-1-benzoazepine-1-carbonyl)benzanilide (**29a**)[11] (2.0 g) in $CHCl_3$ (30 ml) and AcOEt (3.0 ml), and the mixture was stirred vigorously for 3 h at reflux temperature. It was cooled to room temperature, and insoluble material was removed by filtration. The resulting solution was washed with saturated aqueous $NaHCO_3$ and brine, dried, and concentrated. The residue was dissolved in $CHCl_3$ (80 ml), and to the solution was added acetamidine hydrochloride (2.4 g) and K_2CO_3 (4.9 g). The whole was stirred vigorously for 20 h at reflux temperature. It was cooled to room temperature, and washed with water and brine, dried, and concentrated. The residue was crystallized from toluene to give a free amine of **31a** (1.4 g, 64%). The free amine of **31a** (1.0 g) was dissolved in EtOH (10 ml), and to the solution was added a 4 N solution of HCl in AcOEt (0.9 ml) at 0—5 °C. The resulting precipitate was recrystallized from MeOH–MeCN to give **31a** (500 mg, 29%) as a colorless powder, mp 239 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ: 2.33 (3H, s), 2.70 (3H, s), 3.00 (1H, t, J=12 Hz), 3.1—3.3 (2H, m), 5.01 (1H, d, J=11 Hz), 6.88 (1H, d, J=7.3 Hz), 7.01 (2H, d, J=7.8 Hz), 7.14 (1H, t, J=7.6 Hz), 7.2—7.5 (5H, m), 7.56 (2H, d, J=7.8 Hz), 8.17 (1H, d, J=7.3 Hz), 10.40 (1H, s), 14.91 (2H, br). FAB-MS m/z: 437 (M^++1). *Anal.* Calcd for $C_{27}H_{24}N_4O_2 \cdot HCl \cdot H_2O$: C, 66.05; H, 5.54; Cl, 7.22; N, 11.41. Found: C, 66.39; H, 5.48; Cl, 7.31; N, 11.70.

Compounds **31b**—**g** were synthesized in the same manner

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