Nonpeptide Arginine Vasopressin Antagonists for Both V_{1A} and V_2 Receptors: Synthesis and Pharmacological Properties of 2-Phenyl-4′-(2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-carbonyl)benzanilide Derivatives

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A series of compounds structurally related to 2-phenyl-4′-(2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-carbonyl)benzanilide was synthesized and demonstrated to have arginine vasopressin (AVP) antagonist activity for both V_{1A} and V_2 receptors. The introduction of a hydrophilic substituent group into the 5-position of the benzodiazepine ring resulted in an increase in oral availability. Especially, the (3-pyridyl)methyl (31b), the 2-(4-methyl-1,4-diazepan-1-yl)-2-oxoethyl (32i), and the 2-(4-methylpiperazin-1-yl)ethyl (33g) derivatives exhibited high antagonist activities and high oral availability. Details of the synthesis and pharmacological properties of this series are presented.

Key words arginine vasopressin antagonist; benzodiazepine; 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, V_{1A} and V_2, in periphery.[1] The V_{1A} receptor mediates phospholipase C activation and causes the effects of AVP on the cardiovascular system, such as the vasoconstrictive effect on arterial smooth muscles.[1] The V_2 receptor mediates adenylate cyclase and plays a predominant role in the kidney, such as the antidiuretic response to AVP which promotes water reabsorption.[2] From these two major effects are derived the two names for AVP, thus "vasopressin" and "antidiuretic hormone (ADH)".

Therefore, an AVP receptor antagonist could be a good pharmaceutical tool for treating various diseases. Recently, several nonpeptide V_{1A}-selective and V_2-selective antagonists have been reported,[3—6] and some of them are under clinical testing (Fig. 1).

Before starting research on AVP receptor antagonists, we noticed the relationships between AVP and congestive heart failure (CHF). In particular, many reports indicated that AVP plays a role in CHF and that patients with CHF show a high level of plasma AVP.[7,8] A specific peptide V_{1A} receptor antagonist (Manning compound) given intravenously caused a significant hemodynamic improvement in some CHF patients with a high level of plasma AVP. Most CHF patients with hyponatremia showed inappropriate secretion of AVP, and they also had a highly unfavorable long term prognosis.[9] Therefore, the blockade of both V_{1A} and V_2 receptors might be beneficial to such CHF patients.

On the basis of this hypothesis, we have been attempting to develop new AVP antagonists for both V_{1A} and V_2 receptors. In a previous paper,[10] we have reported that 2-phenyl-4′-(2,3,4,5-tetrahydro-1*H*-1-benzoazepine-1-carbonyl)benzanilide derivatives (**1**, Fig. 2) have potent AVP antagonist activities for both V_{1A} and V_2 receptors. However, the oral availability and water solubility of these compounds were not satisfactory for our purpose; then we investigated further focusing on an increase in oral availability and water solubility by introduction of a hydrophilic moiety into **1**.

In this report, replacement of the benzoazepine ring by a more hydrophilic benzodiazepine ring, and introduction of hydrophilic substituent groups onto the benzodiazepine ring were investigated. Herein, the synthesis and the biological activity of these compounds are described.

Chemistry

The synthetic pathway for the preparation of the benzodiazepine derivatives listed in Tables 1—5 is shown in Charts 1—3. 1,4-Benzodiazepine derivatives were synthesized according to the route shown in Chart 1. Condensation of 2-phenylbenzoic acid (**2a**) with ethyl 4-aminobenzoate (**3**) gave benzanilide derivative (**4**), which was then hydrolyzed to give a key intermediate 4-(2-phenylbenzoyl)aminobenzoic acid (**5**). 4-Substituted 1,4-benzodiazepine derivative (**7**) was

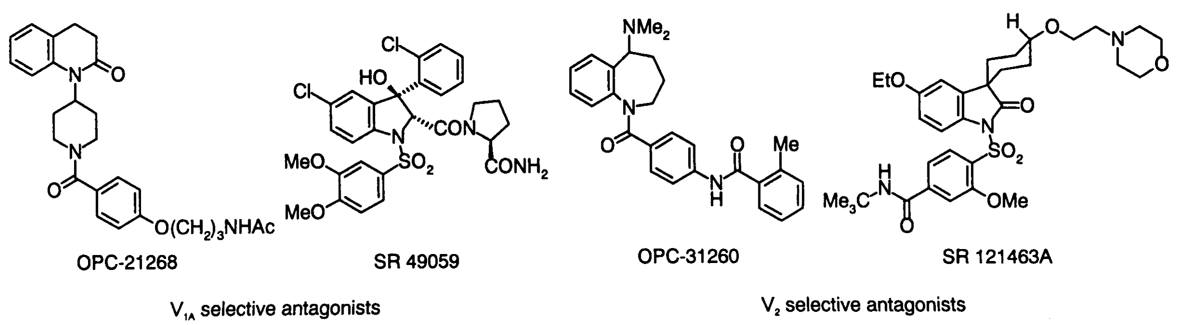

Fig. 1

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prepared by condensation of **5** and 2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (**6**)[11] with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide monohydrochloride (WSC). On the other hand, condensation of **5** and 4-benzyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (**8**)[12] followed by catalytic hydrogenation gave 1-substituted 1,4-benzodiazepine derivative (**10**).

1-(4-Nitrobenzoyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine derivatives which were key intermediates of the desired 1,5-benzodiazepine derivatives, were synthesized according to the routes shown in Chart 2. 1-(4-Nitrobenzoyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (**13**) was prepared by condensation of 2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (**11**)[13] with 4-nitrobenzoyl chloride (**12**). Alkylation of **13** with alkyl halide gave benzyl (**14a**), ethoxycarbonylmethyl (**14b**), and acetamide (**14c**) derivatives (route A). Phenyl derivative (**16**) was prepared by cyclization of 4-nitro-2′-(phenylamino)benzanilide (**15**)[14] and 1,3-dibromopropane with potassium *tert*-butoxide (route B). Pyridylmethyl (**24a**—**c**) and aminoalkyl (**24d**—**l**) derivatives were prepared by two synthetic pathways (route C). Alkylation of 1,3,4,5-tetrahydro-1,5-benzodiazepin-2(2*H*)-one (**17**)[15] with the corresponding alkyl chloride gave 1-substituted 1,3,4,5-tetrahydro-1,5-benzodiazepin-2(2*H*)-one derivatives (**18**). The reduction of the amide group of **18** with lithium aluminum hydride (LAH) or borane tetrahydrofuran (THF) complex afforded 1-substituted 2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine derivatives (**19**). Whereas alkylation of **17** with ethyl bromoacetate followed by hydrolysis gave acetic acid derivative (**21**). Acetamide derivatives (**22**) were prepared by condensation of various amines and **21**. Two amide groups of **22** were reduced in the same manner as **18**, giving 1-substituted 2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine derivatives (**23**). Nitrobenzoyl derivatives **24** were obtained from **19** and **23** in the same manner as **13**.

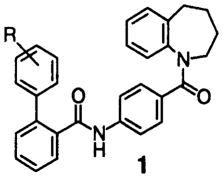


Fig. 2

The desired 1,5-benzodiazepine derivatives were synthesized according to the route shown in Chart 3. Each nitro group of **13**, **14**, **16**, and **24** was reduced by catalytic hydrogenation or with $SnCl_2$, giving aniline derivatives (**25**). 4′-(5-Nonsubstituted 1,5-benzodiazepine-1-carbonyl)benzanilide derivatives (**26**) were prepared by condensation of **25a** and 2-phenylbenzoic acid derivatives (**2**) with WSC. 5-Acyl-substituted 1,5-benzodiazepine derivatives (**27**) were prepared by acylation of **26a** with acetic anhydride or benzoyl chloride. 5-Methyl (**28**), phenyl (**29**), benzyl (**30**), pyridylmethyl (**31**), acetamide (**32a**), aminoalkyl (**33**), and ethoxycarbonylmethyl (**34**)-substituted 1,5-benzodiazepine derivatives were prepared by condensation of **25b**—**q** and the acid chloride of **2a**. Hydrolysis of **34** gave the 5-acetic acid derivative (**35**), which was condensed with various amines to give 5-carbamoylmethyl derivatives (**32b**—**j**).

Results and Discussion

Binding Affinity The methods for determination of *in vitro* AVP and oxytocin (OT) receptor-binding affinities (rat liver for V_{1A}, rabbit kidney for V_2, and rat uterus for OT) are described in the experimental section. The results of the binding assay of the compounds (**7**, **10**, **26**—**33**) are shown in Tables 1—5. In the initial modification, the effect of the replacement of the benzoazepine ring of **1a** by a more hydrophilic benzodiazepine ring was investigated (Table 1). 1,4-Benzodiazepine derivatives (**7**, **10**) showed poor binding affinities. Whereas, the 1,5-benzodiazepine derivative (**26a**) showed almost 10-fold enhanced binding affinities for both V_{1A} and V_2 receptors compared with **1a**. Comparison of the results of **7**, **10**, and **26a** showed that the 1,5-position of the two nitrogen atoms of the benzodiazepine ring might give the best binding affinity for both V_{1A} and V_2 receptors. Compound **26b**, which has a methyl group on the 4′-position of the biphenyl group, showed 5-fold lower binding affinities for both V_{1A} and V_2 receptors compared with **26a**. This result was different from that of the benzoazepine derivatives (**1a**

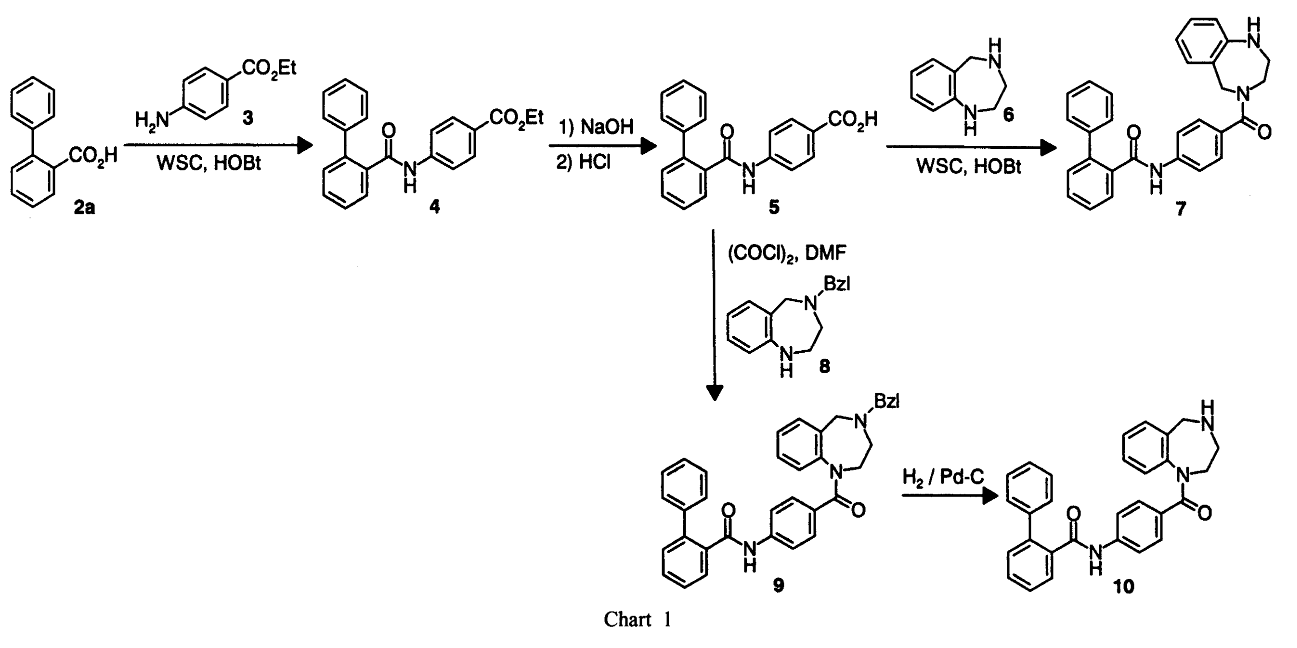


Chart 1

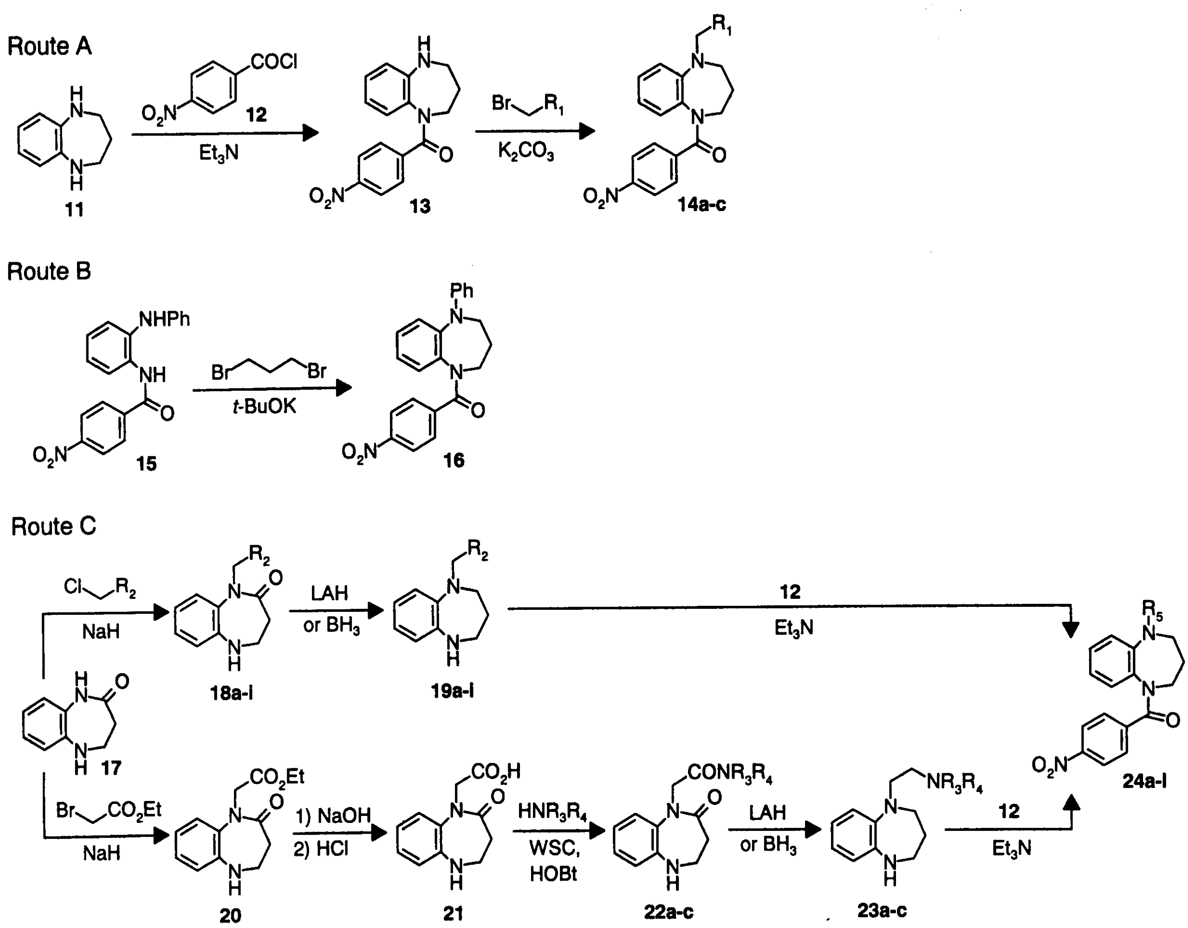


Chart 2

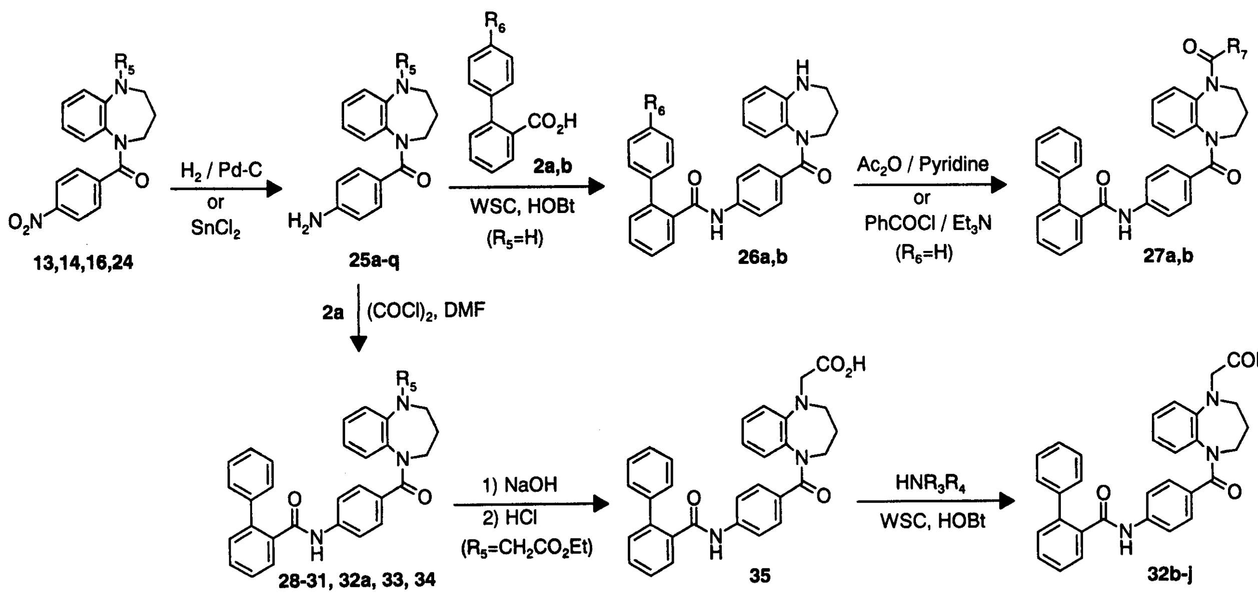


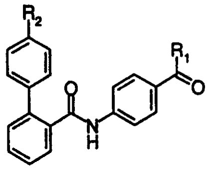
Chart 3

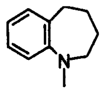
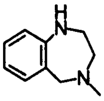
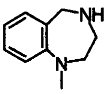
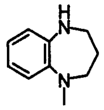
versus **1b**).

On the basis of these studies, 1,5-benzodiazepine derivative **26a** was selected as the new lead compound for further investigation. Therefore, various substituent groups were introduced onto the 5-position of the benzodiazepine moiety of **26a** as the second modification (Table 2). The methyl derivative (**28**) maintained binding affinity potentials; however, the phenyl derivative (**29**) showed over 100-fold less potency than **28**. Because the introduction of acetyl (**27a**), benzoyl (**27b**), and benzyl (**30**) groups led to somewhat recovered binding affinity potentials, increased steric bulkiness adjacent to the 5-position of the benzodiazepine ring might be responsible for decreased binding affinities. Thus, we introduced an alkylene spacer between the hydrophilic group and the benzodiazepine ring to avoid an increase in steric bulkiness. Therefore, pyridylmethyl, carbamoylmethyl, and aminoalkyl derivatives were prepared and tested as the next modification.

Pyridylmethyl-substituted derivatives (**31a**—**c**) are shown

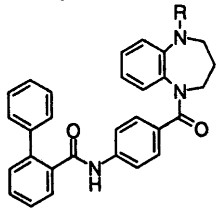
Table 1. Receptor-Binding Affinities for Benzoazepine and Benzodiazepine Derivatives



No.	R_1	R_2	Yield (%)[a]	mp (°C)	Formula[b]	^{1}H-NMR ($CDCl_3$) δ	MS m/z ($M^+ +1$)	Binding affinity (pK_i) V_{1A}[c]	V_2[d]	OT[e]
1a[f]		H						7.85	8.12	7.20
1b[f]		Me						8.07	8.61	7.47
7		H	80	NT[g]	$C_{29}H_{25}N_3O_2 \cdot H_2O$	3.11 (1H, br), 3.30 (1H, br), 3.65 (1H, br), 3.9—4.0 (2H, br), 4.34 (1H, br), 4.68 (1H, br), 6.76 (2H, d), 6.9—7.2 (7H, m), 7.3—7.6 (7H, m), 7.91 (1H, br)	448	5.70	6.14	<5
10		H	50	112—117	$C_{29}H_{25}N_3O_2 \cdot 5/4H_2O$	2.78 (1H, br), 3.1—3.3 (2H, m), 4.0—4.2 (2H, br), 5.09 (1H, br), 6.64 (1H, br), 6.7—7.1 (7H, m), 7.2—7.5 (8H, m), 7.84 (1H, d)	448	6.97	7.24	<5
26a		H	42	219—223	$C_{29}H_{25}N_3O_2 \cdot 1/5H_2O$	1.94 (1H, br), 2.05 (1H, br), 2.86 (1H, br), 2.96 (1H, br), 3.55 (1H, br), 3.93 (1H, br), 5.03 (1H, br), 6.52 (2H, m), 6.7—7.0 (5H, m), 7.12 (2H, d), 7.3—7.6 (7H, m), 7.84 (1H, d)	448	8.84	8.76	7.22
26b		Me	39	185—190	$C_{30}H_{27}N_3O_2$	1.60 (3H, s), 1.94 (1H, br), 2.06 (1H, br), 2.36 (3H, s), 2.86 (1H, br), 3.00 (1H, br), 3.55 (1H, br), 5.03 (1H, br), 6.5—6.6 (2H, m), 6.76 (1H, d), 6.8—7.0 (4H, m), 7.1—7.2 (4H, m), 7.3—7.5 (4H, m), 7.83 (1H, d)	462	8.35	8.33	6.72

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. *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*) See ref. 10. *g*) NT: not tested (amorphous solid).

Table 2. Receptor-Binding Affinities for 5-Substituted 1,5-Benzodiazepine Derivatives



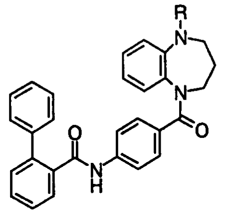
No.	R	Yield (%)[a]	mp (°C)	Formula[b]	^{1}H-NMR ($CDCl_3$) δ	MS m/z ($M^+ +1$)	Binding affinity (pK_i) V_{1A}[c]	V_2[d]	OT[e]
28	Methyl	43	202—207	$C_{30}H_{27}N_3O_2 \cdot 1/5H_2O$	1.82 (1H, br), 2.05 (1H, br), 2.82 (1H, br), 2.92 (3H, s), 3.10 (1H, br), 3.44 (1H, br), 4.61 (1H, br), 6.5—6.6 (2H, m), 6.8—7. 0 (4H, m), 7.0—7.1 (3H, m), 7.3—7.6 (8H, m), 7.83 (1H, d)	462	8.33	8.11	6.75
29	Phenyl	32	177—182	$C_{35}H_{29}N_3O_2 \cdot H_2O$[f]	1.78 (1H, br), 2.21 (1H, br), 3.3—3.8 (3H, m), 4.40 (1H, br), 6.8—7.0 (5H, m), 7.1—7.6 (16H, m), 7.87 (1H, d)	524	5.21	5.80	<5
27a	Acetyl	61	NT[g]	$C_{31}H_{27}N_3O_3 \cdot 1/2H_2O$	1.70 (1H, br), 2.02 (3H, s), 2.09 (1H, br), 2.83 (1H, br), 2.97 (1H, br), 4.73 (1H, br), 6.8—7.6 (16H, m), 7.86 (1H, d)	490	7.00	7.67	6.11
27b	Benzoyl	80	150—155	$C_{36}H_{29}N_3O_3 \cdot H_2O$	1.7—2.1 (2H, br), 2.8—3.3 (3H, br), 4.6—4.9 (1H, br), 6.8—7.7 (21H, m), 7.88 (1H, d)	552	7.04	7.49	6.31
30	Benzyl	51	217—220	$C_{36}H_{31}N_3O_2 \cdot 1/5H_2O$	1.78 (1H, br), 1.98 (1H, br), 2.79 (1H, br), 3.10 (1H, br), 3.40 (1H, br), 4.26 (1H, d), 4.55 (1H, d), 4.66 (1H, br), 6.5—6.6 (2H, m), 6.7—6.9 (3H, m), 7.00 (1H, d), 7.1—7.2 (2H, m), 7.2—7.6 (13H, m), 7.84 (1H, d)	538	8.12	7.38	6.37

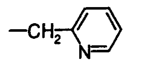
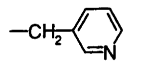
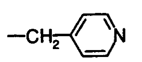
a—*e*) See footnotes in Table 1. *f*) N (Calcd 7.76, Found 7.35). *g*) NT: not tested (amorphous solid).

in Table 3. These compounds showed more potent binding affinities compared to benzyl derivative (**30**), and these affinity potentials increased in the order of 4-pyridyl (**31c**), 3-pyridyl (**31b**), and 2-pyridyl (**31a**) derivatives. From these results, introduction of a basic amino group to **30** was found to enhance the binding affinity potentials.

Carbamoylmethyl-substituted derivatives are shown in Table 4. Primary carbamoylmethyl derivative (**32a**) showed more potent binding affinities for both V_{1A} and V_2 receptors compared with **26a**. *N*-Methyl (**32b**) and *N*,*N*-dimethyl (**32c**)

Table 3. Receptor-Binding Affinities for 5-Pyridylmethyl-Substituted 1,5-Benzodiazepine Derivatives



No.	R	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]
31a[f]		69	220—223	$C_{35}H_{30}N_4O_2 \cdot 1/2H_2O$	1.85 (1H, br), 2.05 (1H, br), 2.94 (1H, br), 3.14 (1H, br), 3.45 (1H, br), 4.46 (1H, d), 4.68 (2H, br), 6.6—7.9 (20H, m), 8.59 (1H, d)	539	8.01	8.11	6.92
31b		61	170—177	$C_{35}H_{30}N_4O_2 \cdot HCl \cdot 1/2H_2O$	1.71 (1H, br), 1.89 (1H, br), 2.85 (1H, br), 3.01 (1H, br), 3.37 (1H, br), 4.47 (1H, d), 4.76 (2H, br), 6.6—7.9 (17H, m), 7.92 (1H, t), 8.45 (1H, d), 8.77 (1H, d), 8.91 (1H, s), 10.28 (1H, s)	539	8.22	8.42	7.34
31c		38	132—137	$C_{35}H_{30}N_4O_2 \cdot C_2H_2O_4 \cdot 1/2H_2O$	1.75 (1H, br), 1.92 (1H, br), 2.85 (1H, br), 3.03 (1H, br), 3.39 (1H, br), 4.36 (1H, d), 4.56 (1H, br), 4.63 (1H, d), 6.64 (2H, s), 7.0—7.6 (17H,m), 8.55 (2H, d)	539	8.45	8.70	7.15

a—e) See footnotes in Table 1. *f*) ^{1}H-NMR Spectra was measured in $CDCl_3$.

derivatives showed a decrease in binding affinity potentials, and pyrrolidine (**32d**) and piperidine (**32e**) derivatives showed still lower binding affinities for both V_{1A} and V_2 receptors. It seemed that increasing the bulkiness of the substituent group trended to decrease the binding affinities. Although acetamide (**32a**) has very potent binding affinities, it was insoluble in water and that was not satisfactory for our purpose.

Then, introduction of a basic amino group to the substituent group of the carbamoylmethyl derivatives was investigated in order to improve the water solubility. Ethylenediamine derivatives (**32f, 32g**) showed recovered binding affinity potential. On the other hand, cyclic amine compounds, such as piperazine (**32h**), 1,4-diazepane (**32i**), and 4-dimethylaminopiperidine (**32j**) derivatives showed lower binding affinities compared with **32f** and **32g**. From these results, it was indicated that increasing the lipophilicity of the substituent group trended to decrease the binding affinity for the V_2 receptor in the case of carbamoylmethyl derivatives.

Aminoalkyl-substituted derivatives, which have the carbamoyl group replaced by an amino group, are shown in Table 5. The results for dialkylamino (**33a—c**), pyrrolidine (**33d**), and piperidine (**33e**) derivatives indicated that increasing bulkiness of the substituent group trended to increase the binding affinities, which were opposite to the results for the carbamoylmethyl derivatives. The lipophilicity of the substituent group seemed less responsible for the binding affinity potentials compared with the case of carbamoylmethyl derivatives. Comparison of **33e** and **33f** indicated that the compound which had an ethylene unit between the amino moiety and the 1,5-benzodiazepine showed more potent binding affinity for the V_2 receptor. From the results of **33g—i**, introduction of a further amine moiety onto the substituent group did not seem responsible for the receptor binding affinity potentials. Amino-substituted carbamoylmethyl (**32f—j**) and aminoalkyl (**33a—i**) derivatives showed an increase in water solubility compared with other carbamoylmethyl derivatives (**32a—e**).

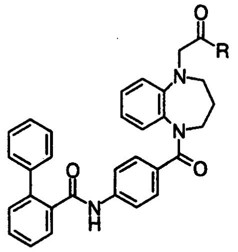
Antagonist Activities V_{1A} receptor antagonist activity was determined by measuring the inhibition of the AVP-induced diastolic blood pressure (DBP) response in pithed rats after intravenous (i.v.) administration. We determined the dose of the compounds causing a 50% inhibition of the pressor response to AVP (ID_{50}). 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 in 2 h after compound dosing (ED_3).

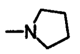
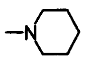
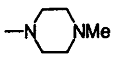
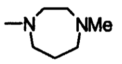
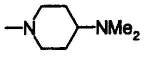
Some compounds which exhibited potent binding affinities for both V_{1A} and V_2 receptors were selected and tested *in vivo* (Table 6). Non-substituted 1,5-benzodiazepine derivative (**26a**), pyridylmethyl derivatives (**31b, 31c**), and carbamoylmethyl derivatives (**32a, 32b, 32i**) showed potent antagonist activities for both V_{1A} and V_2 receptors. Ethylenediamine derivatives (**32f, 32g**) among carbamoylmethyl derivatives and aminoalkyl derivatives exhibited less antagonist activities.

Oral Availability The oral availability was determined by measuring the effect on urine volume in dehydrated conscious rats for V_2 receptor. Among the compounds which showed potent V_2 receptor antagonist activities by i.v. administration, (3-pyridyl)methyl (**31b**), acetamide (**32a**), 2-(4-methyl-1,4-diazepan-1-yl)-2-oxoethyl (**32i**), and 2-(4-methylpiperazin-1-yl)ethyl (**33g**) showed good oral availability; however, non-substituted derivative (**26a**) showed poor oral availability. Whereas, aminoalkyl derivatives (**33b, 33c, 33h**) had good oral availability despite their lower antagonist activity potentials. Then, we attempted to examine the effect of lipophilicity on oral availability of these compounds. However, the relative clog*P* values[16] of these compounds, **33c**>**33b**>**33g**, **33h**, and **31b**>**32i**>**26a**>**32a**, showed that the relationship between lipophilicity and oral availability was not obvious.

Conclusions In this report, 2-phenyl-4′-(2,3,4,5-tetrahy-

Table 4. Receptor-Binding Affinities for 5-Carbamoylmethyl-Substituted 1,5-Benzodiazepine Derivatives



No.	R	Yield (%)[a)]	mp (°C)	Formula[b)]	^{1}H-NMR ($CDCl_3$) δ	MS m/z (M^++1)	Binding affinity (pK_i) V_{1A}[c)]	V_2[d)]	OT[e)]
32a	—NH_2	59	130—135	$C_{31}H_{28}N_4O_3 \cdot H_2O$	1.83 (1H, br), 2.10 (1H, br), 2.91 (1H, br), 3.11 (1H, br), 3.39 (1H, br), 3.74 (1H, d), 4.04 (1H, d), 4.70 (1H, br), 6.5—7.5 (16H, m), 7.83 (1H, d)	505	8.91	9.85	6.27
32b	—NHMe	67	160—165	$C_{32}H_{30}N_4O_3 \cdot 3/2H_2O$[f)]	1.84 (1H, br), 2.08 (1H, br), 2.81 (3H, s), 2.89 (1H, br), 3.13 (1H, br), 3.35 (1H, br), 3.74 (1H, d), 4.04 (1H, d), 4.69 (1H, br), 6.6—7.6 (16H, m), 7.85 (1H, d)	519	8.37	9.06	6.85
32c[g)]	—NMe_2	45	>250	$C_{33}H_{32}N_4O_3 \cdot 1/2H_2O$	1.83 (1H, br), 1.94 (1H, br), 2.86 (3H, s), 3.04 (3H, s), 3.09 (1H, br), 3.58 (2H, m), 4.12 (1H, d), 4.25 (1H, d), 4.46 (1H, br), 6.52 (2H, d), 6.73 (1H, d), 7.0—7.6 (14H, m), 10.26 (1H, s)	533	8.39	9.34	5.97
32d		72	233—237	$C_{35}H_{34}N_4O_3 \cdot 3/4H_2O$	1.8—2.1 (6H, m), 3.18 (2H, br), 3.5—3.7 (5H, m), 3.94 (1H, d), 4.07 (1H, d), 4.62 (1H, br), 6.5—6.6 (2H, m), 6.8—6.9 (4H, m), 7.0—7.1 (3H, m), 7.3—7.6 (7H, m), 7.84 (1H, d)	559	8.72	8.38	7.06
32e		79	220—226	$C_{36}H_{36}N_4O_3 \cdot 1/2H_2O$	1.5—1.7 (6H, m), 1.89 (1H, br), 2.04 (1H, br), 3.05 (1H, br), 3.06 (1H, br), 3.36 (2H, br), 3.5—3.7 (2H, m), 3.73 (1H, br), 3.95 (1H, d), 4.12 (1H, d), 4.60 (1H, br), 6.54 (1H, d), 6.59 (1H, t), 6.82 (1H, d), 6.95 (3H, m), 7.0—7.1 (3H, m), 7.3—7.6 (7H, m), 7.84 (1H, d)	573	8.34	8.44	6.87
32f[g)]	—$NH(CH_2)_2NMe_2$	61	225—227	$C_{35}H_{37}N_5O_3 \cdot C_2H_2O_4 \cdot 1/2H_2O$	1.82 (1H, br), 1.98 (1H, br), 2.50 (6H, s), 3.00 (4H, br), 3.41 (2H, br), 3.54 (1H, br), 3.85 (1H, d), 4.00 (1H, d), 4.51 (1H, br), 6.55 (2H, br), 6.84 (1H, d), 7.0—7.6 (14H, m), 8.16 (1H, br), 10.28 (1H, s)	576	8.64	9.16	6.72
32g[g)]	—$NMe(CH_2)_2NMe_2$	47	170—180	$C_{36}H_{39}N_5O_3 \cdot C_2H_2O_4 \cdot 2H_2O$	1.84 (1H, br), 1.95 (1H, br), 2.77 (6H, s), 3.04 (4H, br), 3.18 (1H, br), 3.64 (1H, br), 4.13 (1H, d), 4.29 (1H, d), 4.48 (1H, br), 6.52 (2H, s), 6.75 (1H, d), 7.00 (1H, m), 7.15 (2H, d), 7.3—7.6 (11H, m), 10.30 (1H, s)	590	9.01	9.00	6.95
32h[g)]		43	162—164	$C_{36}H_{37}N_5O_3 \cdot EC_2H_2O_4 \cdot 3/2H_2O$	1.83 (1H, br), 1.95 (1H, br), 2.06 (3H, s), 2.89 (5H, m), 3.08 (1H, br), 3.5—3.8 (5H, m), 4.19 (1H, d), 4.34 (1H, d), 4.76 (1H, br), 6.53 (2H, d), 6.76 (1H, d), 7.0—7.6 (14H, m), 10.29 (1H, s)	588	8.30	7.46	6.67
32i[g)]		52	170—176	$C_{37}H_{39}N_5O_3 \cdot HCl \cdot H_2O$	1.83 (1H, br), 2.05 (2H, br), 2.77 (3H, s), 3.0—3.7 (9H, m), 4.0—4.6 (4H, br), 6.53 (2H, s), 6.77 (1H, d), 7.03 (1H, m), 7.14 (2H, m), 7.2—7.6 (11H, m), 10.29 (1H, s)	602	8.59	8.56	6.77
32j		44	212—215	$C_{38}H_{41}N_5O_3 \cdot H_2O$	1.44 (2H, m), 1.75 (1H, m), 1.87 (2H, m), 2.05 (1H, m), 2.25 (2H, s), 2.28 (3H, s), 2.31 (1H, m), 2.5—2.7 (1H, m), 2.9—3.3 (3H, m), 3.49 (1H, m), 3.9—4.2 (3H, m), 4.61 (2H, m), 6.5—7.6 (16H, m), 7.84 (1H, d)	616	8.69	8.67	6.73

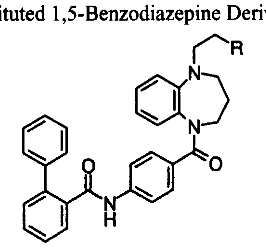
a—e) See footnotes in Table 1. *f*) N (Calcd 10.27, Found 10.76). *g*) ^{1}H-NMR Spectra was measured in DMSO-d_6.

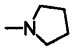
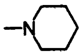
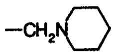
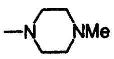
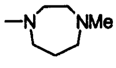
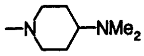
dro-1*H*-1,5-benzodiazepine-1-carbonyl)benzanilide derivatives, which have a substituent group at the 5-position of the benzodiazepine ring, were synthesized in order to develop an orally active AVP antagonist for both V_{1A} and V_2 receptors, and their pharmacological properties were evaluated. As a result, introduction of pyridylmethyl, carbamoylmethyl, and aminoalkyl groups enhanced the *in vitro* and *in vivo* activities. Especially, (3-pyridyl)methyl (**31b**), acetamide (**32a**), 2-(4-methyl-1,4-diazepan-1-yl)-2-oxoethyl (**32i**), and 2-(4-methylpiperazin-1-yl)ethyl (**33g**) showed potent binding affinities and antagonist activities for both V_{1A} and V_2 receptors, with potent oral availability. These compounds except for water-insoluble acetamide (**32a**) suited our purpose. We hope that dual V_{1A} and V_2 receptor antagonists such as **31b**, **32i**, and **33g** 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 a JEOL FX90Q or FX100 spectrometer using tetramethylsilane as an internal standard. MS spectra were determined with a Hitachi M-80 or JEOL JMS-DX300 spectrometer. Elemental analysis data were within ±0.4% of the cal-

Table 5 Receptor-Binding Affinities for 5-Aminoalkyl-Substituted 1,5-Benzodiazepine Derivatives



No.	R	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]
33a	—NMe_2	35	153—156	$C_{33}H_{34}N_4O_2 \cdot 3/2HCl \cdot 3/2H_2O$[f]	1.68 (1H, br), 1.96 (1H, br), 2.81 (6H, s), 3.01 (1H, br), 3.33 (1H, br), 3.55 (4H, m), 3.77 (1H, br), 4.42 (1H, br), 6.6—7.6 (18H, m)	519	8.00	7.95	6.58
33b	—NEt_2	41	NT[g]	$C_{35}H_{38}N_4O_2 \cdot 4/3HCl \cdot 2H_2O$[h]	1.1—1.3 (6H, m), 1.69 (1H, br), 1.99 (1H, br), 2.79 (1H, br), 3.02 (1H, br), 3.2—3.3 (6H, m), 3.49 (2H, br), 3.83 (2H, br), 4.41 (1H, br), 6.6—7.6 (18H, m)	547	8.27	8.29	6.42
33c	—N(isoPr)$_2$	51	NT	$C_{37}H_{42}N_4O_2 \cdot 4/3HCl \cdot 3/2H_2O$[i]	1.2—1.4 (12H, m), 1.70 (1H, br), 1.99 (1H, br), 2.82 (1H, br), 3.01 (1H, br), 3.19 (1H, br), 3.58 (2H, m), 3.80 (4H, br), 4.43 (1H, br), 6.6—6.8 (2H, m), 7.0—7.6 (16H, m)	575	8.62	8.28	6.34
33d		48	148—155	$C_{35}H_{36}N_4O_2 \cdot 2HCl \cdot 2H_2O$	1.69 (1H, br), 1.84 (2H, br), 1.99 (3H, br), 2.79 (1H, br), 3.07 (3H, br), 3.4—3.7 (6H, m), 3.77 (1H, br), 4.43 (1H, br), 6.67 (2H, d), 7.03 (2H, d), 7.14 (1H, m), 7.3—7.7 (11H, m), 10.31 (1H, s)	545	8.58	8.49	6.41
33e		50	195—200	$C_{36}H_{38}$N4$O_2 \cdot HCl \cdot 3/2H_2O$	1.33 (1H, br), 1.6—1.7 (6H, m), 1.95 (1H, br), 2.76 (1H, br), 2.97 (3H, br), 3.30 (2H, m), 3.47 (3H, br), 3.64 (1H, br), 3.84 (1H, br), 4.42 (1H, br), 6.67 (2H, d), 7.02 (2H, d), 7.14 (1H, m), 7.3—7.7 (11H, m), 10.31 (1H, s)	559	8.53	8.90	5.96
33f		58	145—152	$C_{37}H_{40}N_4O_2 \cdot HCl \cdot 3H_2O$[j]	1.36 (1H, br), 1.6—1.7 (6H, m), 2.05 (3H, m), 2.81 (3H, m), 3.0—3.2 (4H, m), 3.35 (2H, d), 3.45 (2H, br), 4.43 (1H, br), 6.63 (2H, br), 7.02 (3H, m), 7.14 (1H, m), 7.3—7.7 (11H, m),10.33 (1H, s)	573	8.58	7.88	6.69
33g		49	202—210	$C_{36}H_{39}N_5O_2 \cdot 2HCl \cdot 3/2H_2O$	1.70 (1H, br), 1.95 (1H, br), 2.80 (3H, s), 3.2—3.9 (14H, m), 4.44 (1H, br), 6.66 (2H, m), 7.03 (2H, m), 7.13 (2H, m), 7.3—7.7 (11H, m)	574	8.78	8.16	6.70
33h		20	177—183	$C_{37}H_{41}N_5O_2 \cdot 2HCl \cdot 2H_2O$	1.70 (1H, br), 1.95 (1H, br), 2.19 (2H, br), 2.78 (3H, s), 3.01 (1H, br), 3.4—3.5 (10H, m), 3.78 (4H, br), 4.45 (1H, br), 6.66 (2H, d), 7.03 (2H, d), 7.14 (1H, s), 7.3—7.7 (11H, m), 10.32 (1H, s)	588	8.44	8.68	6.94
33i		41	172—180	$C_{38}H_{43}N_5O_2 \cdot 5/2HCl \cdot 7/2H_2O$	1.70 (1H, br), 1.9—2.3 (6H, m), 2.69 (6H, s), 3.06 (3H, br), 3.35 (3H, br), 3.50 (2H, br), 3.71 (1H, br), 3.84 (2H, m), 4.44 (1H, br), 6.66 (2H, m), 7.03 (2H, m), 7.15 (2H, m), 7.3—7.7 (11H, m), 10.33 (1H, s)	602	8.84	8.13	6.78

a) Yields were based on the final two steps (**33a**—**c**) and final step (**33d**—**i**) of the synthetic method and were not optimized. *b*—*e*) See footnotes in Table 1. *f*) C (Calcd 66.02, Found 65.55). *g*) NT: not tested (Amorphous solid). *h*) H (Calcd 6.92, Found 6.49). *i*) C (Calcd 68.33, Found 78.76). *j*) H (Calcd 6.91, Found 6.37).

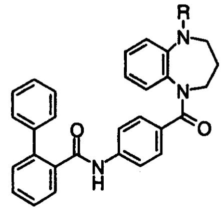
culated values unless otherwise noted. Chromatographic purification was performed on Merck KGaA Silica gel 60 (0.040—0.063 mm).

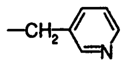
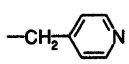
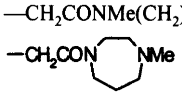
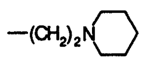
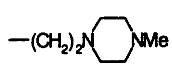
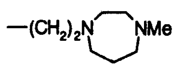
Ethyl 4-(2-Phenylbenzoyl)aminobenzoate (4) A mixture of 2-phenylbenzoic acid (**2a**) (1.98 g), ethyl 4-aminobenzoate (**3**) (1.65 g), WSC (2.88 g), and 1-hydroxybenzotriazole (HOBt) (2.0 g) in THF (20 ml) was stirred for 10 d at room temperature. It was poured into water, and the whole was extracted with ethyl acetate (AcOEt). The organic layer was washed with 1 N NaOH, 1 N HCl, and brine, dried, and concentrated. The residue was chromatographed over silica gel using 1 : 1 $CHCl_3$–hexane and crystallized from ethanol (EtOH) to give **4** (280 mg, 8.1%) as a colorless powder, mp 113—116 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.36 (3H, t), 4.34 (2H, q), 6.9—7.1 (2H, m), 7.24 (2H, d), 7.4—7.7 (5H, m), 7.8—8.0 (4H, m). FAB-MS m/z: 346 (M^++1). *Anal.* Calcd for $C_{22}H_{19}NO_3$: C, 76.50; H, 5.54; N, 4.06. Found: C, 76.45; H, 5.54; N, 4.05.

4-(2-Phenylbenzoyl)aminobenzoic Acid (5) A mixture of a solution of **4** (280 mg) in EtOH (10 ml) and 1 N NaOH (1.5 ml) was stirred for 18 h at room temperature, then concentrated. The residue was dissolved in water. This solution was washed with diethyl ether (Et_2O), then treated with 1 N HCl. The resulting precipitate was collected by filtration and washed with water to give **5** (220 mg, 86%) as a colorless powder, mp 246—248 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.3—7.8 (10H, m), 7.91 (2H, d), 8.4 (1H, br). FAB-MS m/z: 318 (M^++1). *Anal.* Calcd for $C_{20}H_{15}NO_3$: C,75.70; H, 4.76; N, 4.41. Found: C, 75.87; H, 4.82; N, 4.26.

2-Phenyl-4′-(2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine-4-carbonyl)benzanilide (7) A mixture of **5** (320 mg), WSC (210 mg), HOBt (160 mg), and 2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (**6**)[11] (150 mg) in *N*,*N*-dimethylformamide (DMF) (5 ml) was stirred for 1 h at room temperature. It was 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 100 : 1 $CHCl_3$–methanol (MeOH) and crystallized from Et_2O to give **7** (360 mg, 80%) as a colorless amorphous solid. ^{1}H-NMR ($CDCl_3$) δ: 3.11 (1H, br), 3.30 (1H, br), 3.65 (1H, br), 3.9—4.0 (2H, br), 4.34 (1H, br), 4.68 (1H, br), 6.76 (2H, d), 6.9—7.2 (7H, m), 7.3—7.6 (7H, m), 7.91 (1H, br). FAB-MS m/z: 448 (M^++1). *Anal.* Calcd for $C_{29}H_{25}N_3O_2 \cdot H_2O$: C, 74.82; H, 5.85; N, 9.03. Found: C, 74.91; H, 5.85; N, 9.01.

Table 6. AVP-Antagonist Activities and Oral Availability for 1,5-Benzodiazepine Derivatives



No.	R	Binding affinity (pK_i)		Antagonist activity		Oral availability
		V_{1A}	V_2	V_{1A} ID_{50} (mg/kg)[a)]	V_2 ED_3 (mg/kg)[b)]	UV (ml)[c)]
26a	—H	8.84	8.76	0.027	0.26	0.76±0.34
31b		8.22	8.42	0.021	0.62	6.97±0.44
31c		8.45	8.70	0.087	0.38	4.85±0.56
32a	—CH_2CONH_2	8.91	9.85	0.041	0.21	6.95±0.49
32b	—$CH_2CONHMe$	8.37	9.06	0.052	0.31	1.12±0.20
32f	—$CH_2CONH(CH_2)_2NMe_2$	8.64	9.16	0.16	0.34	3.15±0.59
32g	—$CH_2CONMe(CH_2)_2NMe_2$	9.01	9.00	0.16	0.66	3.73±0.40
32i		8.59	8.56	0.072	0.34	6.84±1.07
33b	—$(CH_2)_2NEt_2$	8.27	8.29	0.24	0.89	8.13±0.70
33c	—$(CH_2)_2N(isoPr)_2$	8.62	8.28	0.092	1.22	7.09±0.76
33e		8.53	8.90	0.25	0.92	3.46±0.24
33g		8.78	8.16	0.12	0.25	6.99±1.18
33h		8.44	8.68	0.22	0.95	8.68±0.36

a) ID_{50} represents the drug concentration (mg/kg) required to inhibit AVP-induced pressor response in pithed rats by 50% by 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. *c)* UV values mean urine volume (ml) during 2 h after oral administration of the drug (10 mg/kg) to rats and are expressed as mean±S.E.M.

4′-(4-Benzyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine-1-carbonyl)-2-phenylbenzanilide (9) To an ice-cooled solution of **5** (760 mg) in CH_2Cl_2 (20 ml) were added a catalytic amount of DMF and oxalyl chloride (280 mg), and the mixture was stirred for 1 h. It was concentrated and the residue was dissolved in THF (20 ml). This solution was added dropwise to an ice-cooled solution of 4-benzyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (**8**)[12] (480 mg) and Et_3N (200 mg) in THF (20 ml), and the mixture was stirred for 1 h. To the mixture was added $CHCl_3$, and it was washed with saturated aqueous $NaHCO_3$ and brine, dried, and concentrated. The residue was chromatographed over silica gel using $CHCl_3$ and crystallized from AcOEt to give **9** (270 mg, 25%) as a colorless powder, mp 122—127 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.10 (3H, m), 3.59 (1H, d), 3.68 (1H, d), 3.80 (1H, d), 4.15 (1H, d), 4.92 (1H, br), 6.01 (1H, d), 6.8—7.1 (7H, m), 7.2—7.6 (13H, m), 7.84 (1H, d). FAB-MS *m/z*: 538 (M^++1). *Anal.* Calcd for $C_{36}H_{31}N_3O_2 \cdot H_2O$: C, 77.81; H, 5.99; N,7.56. Found: C, 78.16; H, 5.85; N, 7.32.

2-Phenyl-4′-(2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine-1-carbonyl)benzanilide (10) A mixture of **9** (430 mg) and 10% Pd-C (50 mg) in acetic acid (AcOH) (20 ml) was stirred under a hydrogen atmosphere (1 atm) at room temperature. After absorption of 18 ml of hydrogen, the catalyst was removed by filtration, and the filtrate was concentrated. To the residue was added water, and the resulting solution was made basic with 1 N NaOH. The mixture was extracted with $CHCl_3$. The organic layer was washed with brine, dried, and concentrated. The residue was chromatographed over silica gel using 50 : 1 $CHCl_3$–MeOH and crystallized from Et_2O to give **10** (180 mg, 50%) as a colorless powder, mp 112—117 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.78 (1H, br), 3.1—3.3 (2H, m), 4.0—4.2 (2H, br), 5.09 (1H, br), 6.64 (1H, br), 6.7—7.1 (7H, m), 7.2—7.5 (8H, m), 7.84 (1H, d). FAB-MS *m/z*: 448 (M^++1). *Anal.* Calcd for $C_{29}H_{25}N_3O_2 \cdot 5/4H_2O$: C, 74.10; H, 5.90; N, 8.94. Found: C, 74.33; H, 5.68; N,8.66.

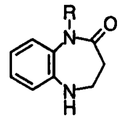
1-(4-Nitrobenzoyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (13) A solution of 4-nitrobenzoyl chloride (**12**) (2.96 g) in CH_2Cl_2 (15 ml) was added dropwise to a solution of 2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (**11**)[13] (2.36 g) and Et_3N (2.21 ml) in CH_2Cl_2 (50 ml) at 0—5 °C, and the mixture was stirred for 30 min at this temperature. It was poured into saturated aqueous $NaHCO_3$, and the whole was extracted with CH_2Cl_2. The organic layer was washed with brine, dried, and concentrated. The residue was crystallized from AcOEt to give **13** (4.11 g, 87%) as a yellow powder, mp 160—162 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.8—2.4 (2H, br), 2.7—3.3 (2H, br), 3.5—3.8 (1H, br), 4.9—5.2 (1H, m), 6.5—7.1 (4H, m), 7.42 (2H, d), 7.99 (2H, d). FAB-MS *m/z*: 298(M^++1). *Anal.* Calcd for $C_{16}H_{15}N_3O_3$: C, 64.64; H, 5.09; N, 14.13. Found: C, 64.50; H, 4.90; N, 14.09.

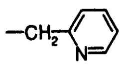
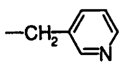
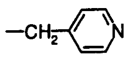
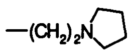
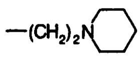
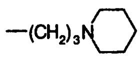
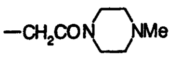
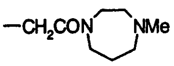
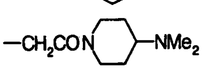
1-Benzyl-5-(4-nitrobenzoyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (14a) Benzyl bromide (600 μl) was added to a solution of **13** (600 mg) and K_2CO_3 (350 mg) in DMF (12 ml), and the mixture was stirred for 10 h at 60 °C. It was cooled and poured into water, and the whole was extracted with AcOEt. The organic layer was washed with brine, dried, and concentrated. The residue was chromatographed over silica gel using 5 : 1 hexane–AcOEt to give **14a** (690 mg, 89%) as a yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.83 (1H, m), 2.06 (1H, m), 2.86 (1H, m), 3.15 (1H, m), 3.44 (1H, m), 4.28 (1H, d), 4.59 (1H, d), 4.70 (1H, m), 6.60 (2H, m), 7.0—7.5 (9H, m), 7.92 (2H, d). FAB-MS *m/z*: 388(M^++1).

In the same manner, compounds **14b** and **14c** were synthesized (reaction conditions: 18 h at 100 °C for **14b**; 18 h at 80 °C for **14c**).

1-(4-Nitrobenzoyl)-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (16) 1,3-Dibromopropane (760 μl) was added to a solution of 4-nitro-2′-(phenylamino)benzanilide (**15**)[14] (1.67 g) and potassium *tert*-butox-

Table 7. Physical and Spectral Data of 1-Substituted 1,5-Benzodiazepin-2-one Derivatives



No.	R	Yield (%)[a]	mp (°C)	Formula[b]	^{1}H-NMR ($CDCl_3$) δ	MS m/z (M^++1)
18a		70	108—110	$C_{15}H_{15}N_3O$	2.64 (2H, t), 3.84 (2H, t), 5.20 (2H, s), 6.9—7.6 (7H, m), 8.51 (1H, d)	254
18b		85	97—99	$C_{15}H_{15}N_3O \cdot 1/5H_2O$	2.61 (2H, t), 3.80 (2H, s), 5.09 (2H, s),6.8—7.2 (5H, m), 7.65 (1H, d), 8.43 (1H, d), 8.50 (1H, s)	254
18c		76	106—108	$C_{15}H_{15}N_3O$	2.64 (2H, t), 3.84 (2H, t), 5.08 (2H, s), 6.88 (1H, d), 6.9—7.1 (3H, m), 7.23 (2H, d), 8.48 (2H, d)	254
18d	—$(CH_2)_2NMe_2$	67	NT	NT	2.23 (6H, s), 2.4—2.6 (4H, m), 3.6—4.0 (4H, m), 6.8—7.3 (4H, m)	233[c]
18e	—$(CH_2)_2NEt_2$	86	NT	NT	0.99 (6H, t), 2.5—2.7 (8H, m), 3.6—3.7 (4H, m), 3.9—4.0 (4H, m), 6.8—6.9 (1H, m), 7.0—7.1 (2H, m), 7.2—7.3 (1H, m)	261[c]
18f	—$(CH_2)_2N(isoPr)_2$	48	NT	NT	1.02 (12H, br), 1.6—1.8 (2H, br), 2.60 (2H, br), 2.98 (2H, br), 3.7—3.8 (4H, m), 6.86 (1H, d), 7.0—7.2 (2H, m), 7.3—7.4 (1H, m)	289[c]
18g		Quant.	NT	NT	2.4—2.5 (6H, m), 2.66 (2H, m), 3.64 (2H, t), 3.98 (2H, m), 6.90 (1H, d), 7.0—7.1 (2H, m),7.25 (1H, m)	260
18h		Quant.	NT	NT	1.25 (2H, br), 1.39 (6H, m), 2.37 (2H, br), 2.46 (4H, m), 3.69 (2H, t), 3.95 (2H, t), 6.91 (1H, d), 7.0—7.1 (2H, m), 7.30 (1H, d)	274
18i		Quant.	NT	NT	1.38 (2H, br), 1.5—1.6 (4H, m), 1.72 (2H, m), 2.29 (6H, m), 2.49 (2H, t), 3.74 (2H, t), 3.87 (2H, t), 6.84 (1H, d), 7.0—7.1 (2H, m), 7.20 (1H, d)	288
20	—CH_2CO_2Et	58	101—103	$C_{13}H_{16}N_2O_3$	1.29 (3H, t), 2.61 (2H, t), 3.78 (2H, t), 4.24 (2H, q), 4.45 (2H, s), 6.88 (2H, d), 7.0—7.1 (3H, m)	249
21[e]	—CH_2CO_2H	19	192—198	$C_{11}H_{12}N_2O_3 \cdot 1/2H_2O$[d]	2.51 (2H, t), 3.69 (2H, t), 4.30 (2H, s), 6.9—7.0 (2H, m), 7.0—7.1 (2H, m)	221
22a		65	NT	NT	2.31 (3H, s), 2.4—2.5 (4H, m), 2.62 (2H, t), 3.53 (2H, br), 3.66 (2H, br), 3.76 (2H, t), 4.58 (2H, s), 6.88 (2H, d), 7.0—7.1 (2H, m), 7.20 (1H, d)	303
22b		Quant.	NT	NT	1.8—2.2 (2H, m), 2.38 (3H, d), 2.5—2.8 (5H, m), 3.5—3.9 (8H, m), 4.53 (2H, s), 6.8—7.3 (4H, m)	317
22c		54	NT	NT	1.4—1.6 (2H, m), 1.8—1.9 (3H, br), 2.29 (3H, s), 2.3—2.4 (1H, m), 2.6—2.7 (3H, m), 3.09 (1H, t), 3.76 (2H, t), 3.86 (1H, d), 4.5—4.6 (3H, m), 6.88 (2H, d), 7.0—7.1 (2H, m), 7.20 (1H, d)	331

a, b) See footnotes in Table 1. *c*) EI-MS (M^+). *d*) H (Calcd 5.72, Found 5.26). *e*) ^{1}H-NMR Spectra was measured in DMSO-d_6. NT: not tested (oil).

ide (560 mg) in DMF (40 ml) at 0—5 °C, and the mixture was stirred for 18 h at 60 °C. It was cooled and poured into 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 5 : 1 hexane–AcOEt and crystallized from Et_2O to give **16** (460 mg, 25%) as a yellow powder, mp 160—163 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.7—2.3 (2H, br), 3.2—3.8 (4H, br), 6.4—7.5 (11H, m), 8.03 (2H, d). FAB-MS m/z: 374 (M^++1). *Anal.* Calcd for $C_{22}H_{19}N_3O_3$: C, 70.76; H, 5.13; N, 11.25. Found: C, 70.56; H, 5.13; N, 11.17.

1-(2-Pyridylmethyl)-1,3,4,5-tetrahydro-1,5-benzodiazepin-2(2*H*)-one (18a) 60% Sodium hydride in mineral oil (0.5 g) was added to an ice-cooled solution of 1,3,4,5-tetrahydro-1,5-benzodiazepin-2(2*H*)-one (**17**)[15] (1.0 g) in DMF (20 ml), and the mixture was stirred for 10 min at ice bath temperature and 10 min at room temperature. To this mixture was added 2-(chloromethyl)pyridine monohydrochloride (1.0 g) at 0—5 °C, and stirred for 1.5 h at this temperature. It was poured into ice-water, and this mixture was made basic with 1 N NaOH. The whole was extracted with $CHCl_3$. The organic layer was washed with brine, dried, and concentrated. The residue was chromatographed over silica gel using 30 : 1 $CHCl_3$–MeOH and crystallized from Et_2O to give **18a** (1.09 g, 70%) as a colorless powder, mp 108—110 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.64 (2H, t), 3.84 (2H, t), 5.20 (2H, s), 6.9—7.6 (7H, m), 8.51 (1H, d). FAB-MS m/z: 254 (M^++1). *Anal.* Calcd for $C_{15}H_{15}N_3O$: C, 71.13; H, 5.97; N, 16.59. Found: C, 71.13; H, 6.04; N, 16.53.

In the same manner, compounds **18b**—**i** were synthesized (reaction conditions: 1.5 h at 0—5 °C for **18b** and **18c**; 18 h at room temperature for **18e**, **18f**, and **18i**; 6 h at 50 °C for **18g** and **18h**; 18 h at 80 °C for **18d**).

1-(2-Pyridylmethyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (19a) **18a** (1.2 g) was added to a solution of 1 M borane in THF (25 ml), and the mixture was stirred for 5 h at reflux temperature. After cooling, MeOH (5 ml) was added and the mixture was stirred for 30 min at room temperature. To this mixture was added concentrated hydrochloric acid (5 ml), and the mixture was stirred for 30 min at room temperature. It was concentrated, and the residue was washed with Et_2O and then made basic with 1 N NaOH. The whole was extracted with $CHCl_3$. The organic layer was washed with brine, dried, and concentrated. The residue was chromatographed over silica gel using 30 : 1 $CHCl_3$–MeOH and crystallized from hexane to give **19a** (410 mg, 36%) as a colorless powder, mp 95—97 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.81 (2H, m), 3.22 (4H, m), 4.55 (2H, s), 6.6—6.9 (4H, m), 7.16 (1H, m), 7.49 (1H, d), 7.65 (1H, m), 8.56 (1H, m). FAB-MS m/z: 240 (M^++1). *Anal.* Calcd for $C_{15}H_{17}N_3 \cdot 1/10H_2O$: C, 74.72; H, 7.19; N, 17.43. Found: C, 74.65; H, 7.37; N, 17.46.

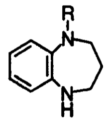
In the same manner, compounds **19b**, **19c** and **19g**—**i** were synthesized.

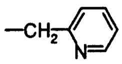
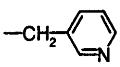
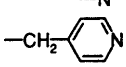
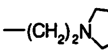
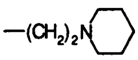
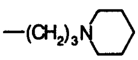
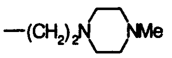
1-(2-Dimethylaminoethyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (19d) 1-(2-Dimethylaminoethyl)-1,3,4,5-tetrahydro-1,5-benzodiazepin-2(2*H*)-one (**18d**) (960 mg) was added to a suspension of LAH (310 mg) in THF (10 ml), and the mixture was stirred for 18 h at reflux temperature. After cooling, MeOH (5 ml) was added dropwise and the mixture was concentrated. The residue was washed with Et_2O and then made basic with 1 N NaOH. The whole was extracted with $CHCl_3$. The organic layer was washed with brine, dried, and concentrated to give **19d** (600 mg, 66%) as a colorless oil. ^{1}H-NMR($CDCl_3$) δ: 2.00 (6H, m), 3.0—4.0 (10H, m), 6.8—7.3 (4H, m). EI-MS m/z: 219(M^+).

In the same manner, compounds **19e** and **19f** were synthesized.

Ethyl (1,3,4,5-Tetrahydro-1,5-benzodiazepin-2(2*H*)-on-1-yl)acetate (20) 60% Sodium hydride in mineral oil (1.3 g) was added to an ice-cooled solution of **17** (4.9 g) in DMF (140 ml), and the mixture was stirred for 30 min at

Table 8. Physical and Spectral Data of 1-Substituted 1,5-Benzodiazepin Derivatives



No.	R	Yield (%)[a)]	mp (°C)	Formula[b)]	^{1}H-NMR($CDCl_3$) δ	MS m/z (M^++1)
19a		36	95—97	$C_{15}H_{17}N_3\cdot1/10H_2O$	1.81 (2H, m), 3.22 (4H, m),4.55 (2H, s), 6.6—6.9 (4H, m), 7.16 (1H, m), 7.49 (1H, d), 7.65 (1H, m), 8.56 (1H, m)	240
19b		50	89—90	$C_{15}H_{17}N_3\cdot1/4H_2O$	1.74 (2H, m), 3.06 (2H, t), 3.20 (2H, t), 4.38 (2H, s), 6.7—6.9 (4H, m), 7.26 (1H, m), 7.76 (1H, d), 8.51 (1H, d), 8.63 (1H, br)	240
19c		76	120—121	$C_{15}H_{17}N_3$	1.79 (1H, m), 3.12 (2H, t), 3.23 (2H, t), 4.39 (2H, s), 6.7—6.8 (4H, m), 7.33 (2H, d), 8.55 (2H, d)	240
19d	—$(CH_2)_2NMe_2$	66	NT	NT	2.00 (6H, m), 3.0—4.0 (10H, m), 6.8—7.3 (4H, m)	219[c)]
19e	—$(CH_2)_2NEt_2$	96	NT	NT	1.08 (6H, t), 1.7—2.0 (2H, m), 2.68 (4H, q), 2.80 (2H, m), 3.15 (4H, t), 3.37 (2H, m), 6.4—7.0 (4H, m)	247[c)]
19f	—$(CH_2)_2N(isoPr)_2$	Quant.	NT	NT	1.10 (12H, d), 1.8—2.0 (2H, m), 2.74 (2H, m), 3.0—3.5 (8H, m), 6.4—7.0 (4H, m)	275[c)]
19g		78	NT	NT	1.8—1.9 (8H, m), 2.58 (2H, br), 2.74 (4H, t), 3.15 (4H, m), 3.40 (2H, t), 6.65 (2H, d), 6.7—6.8 (2H, m), 6.91 (1H, d)	246
19h		82	NT	NT	1.44 (2H, m), 1.5—1.6 (4H, m), 1.85 (2H, t), 2.45 (4H, br), 2.58 (2H, t), 3.14 (4H, q), 3.35 (2H, t), 6.64 (2H, d), 6.7—6.8 (2H, m), 6.91 (1H, d)	259[c)]
19i		63	NT	NT	1.44 (2H, br), 1.5—1.6 (4H, m), 1.8—1.9 (4H, m), 2.38 (6H, br), 3.1—3.2 (6H, m), 6.64 (2H, d), 6.7—6.8 (2H, m), 6.88 (1H, d)	274
23a		91	NT	NT	1.85 (2H, t), 2.29 (3H, s), 2.4—2.6 (8H, br), 3.15 (4H, t), 3.33 (2H, t), 6.64 (2H, d), 6.7—6.8 (2H, m), 6.91 (1H, d)	275

a, b) See footnotes in Table 1. *c)* EI-MS (M^+). NT: not tested (oil).

0—5 °C and 10 min at room temperature. To this mixture was added a solution of ethyl bromoacetate (5.0 g) in DMF (6.5 ml) at 0—5 °C, and the mixture was stirred for 30 min at this temperature. It was poured into ice-water, and the whole was extracted with AcOEt. The organic layer was washed with brine, dried, and concentrated. The residue was crystallized from Et_2O to give **20** (4.3 g, 58%) as a colorless powder, mp 101—103 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.29 (3H, t), 2.61 (2H, t), 3.78 (2H, t), 4.24 (2H, q), 4.45 (2H, s), 6.88 (2H, d), 7.0—7.1 (3H, m). FAB-MS m/z: 249(M^++1). *Anal.* Calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.77; H, 6.38; N, 11.23.

(1,3,4,5-Tetrahydro-1,5-benzodiazepin-2(2*H*)-on-1-yl)acetic Acid (21) 1 N NaOH (24 ml) was added to a solution of **20** (5.9 g) in EtOH (120 ml), and the mixture was stirred for 3 h at room temperature. It was concentrated, and the residue was acidified with 1 N HCl. The whole was extracted with $CHCl_3$. The organic layer was washed with brine, dried, and concentrated. The residue was filtrated and washed with Et_2O to give **21** (970 mg, 19%) as a colorless powder, mp 192—198 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.51 (2H, t), 3.69 (2H, t), 4.30 (2H, s), 6.9—7.0 (2H, m), 7.0—7.1 (2H, m). FAB-MS m/z: 221 (M^++1). *Anal.* Calcd for $C_{11}H_{12}N_2O_3\cdot1/2H_2O$: C, 57.64; H, 5.72; N, 12.22. Found: C, 57.30; H, 5.26; N, 12.01.

1-[2-(4-Methylpiperazin-1-yl)-2-oxoethyl]-1,3,4,5-tetrahydro-1,5-benzodiazepin-2(2*H*)-one (22a) A mixture of **21** (1.0 g), 1-methylpiperazine (400 mg), WSC (770 mg), and HOBt (570 mg) in THF (20 ml) was stirred for 18 h at room temperature. It was concentrated, and the residue was dissolved in $CHCl_3$. The solution was washed with brine, dried, and concentrated. The residue was chromatographed over silica gel using 5 : 1 $CHCl_3$–MeOH to give **22a** (790 mg, 65%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 2.31 (3H, s), 2.4—2.5 (4H, m), 2.62 (2H, t), 3.53 (2H, br), 3.66 (2H, br), 3.76 (2H, t), 4.58 (2H, s), 6.88 (2H, d), 7.0—7.1 (2H, m), 7.20 (1H, d). FAB-MS m/z: 303 (M^++1).

In the same manner, compounds **22b** and **22c** were synthesized.

1-[2-(4-Methylpiperazin-1-yl)ethyl]-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (23a) **22a** (1.2 g) was added to a solution of 1 M borane in THF (30 ml), and the mixture was stirred for 7 h at reflux temperature. After cooling, MeOH (5 ml) was added and the mixture was stirred for 30 min at room temperature. To this mixture was added concentrated hydrochloric acid (5 ml) and the mixture was stirred for 20 min at reflux temperature. It was concentrated, and the residue was dissolved in water. The solution was washed with Et_2O, and then made basic with 1 N NaOH. The whole was extracted with $CHCl_3$. The organic layer was washed with brine, dried, and concentrated to give **23a** (600 mg, 91%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.85 (2H, t), 2.29 (3H, s), 2.4—2.6 (8H, br), 3.15 (4H, t), 3.33 (2H, t), 6.64 (2H, d), 6.7—6.8 (2H, m), 6.91 (1H, d). FAB-MS m/z: 275 (M^++1).

1-(4-Nitrobenzoyl)-5-(2-pyridylmethyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (24a) **12** (440 mg) was added to an ice-cooled solution of **19a** (560 mg) and Et_3N (330 μl) in CH_2Cl_2 (15 ml) at 0—5 °C, and the mixture was stirred for 1 h at this temperature. It was poured into saturated aqueous $NaHCO_3$, and the whole was extracted with CH_2Cl_2. The organic layer was washed with brine, dried, and concentrated. The residue was crystallized from Et_2O to give **24a** (800 mg, 88%) as a yellow powder, mp 142—144 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.90 (1H, m), 2.10 (1H, m), 3.00 (1H, m), 3.20 (1H, m), 3.50 (1H, m), 4.47 (1H, d), 4.70 (2H, m), 6.60 (2H, br), 7.0—7.5 (6H, m), 7.70 (1H, t), 7.90 (2H, d), 8.61 (1H, d). FAB-MS m/z: 389 (M^++1). *Anal.* Calcd for $C_{22}H_{20}N_4O_3$: C, 68.03; H, 5.19; N, 14.42. Found: C, 67.85; H, 5.17; N, 14.18.

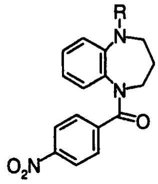
In the same manner, compounds **24b—j** were synthesized.

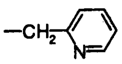
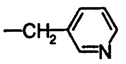
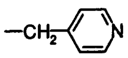
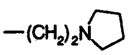
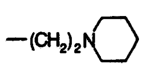
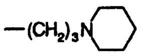
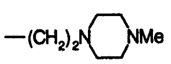
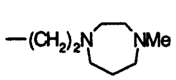
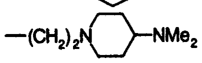
1-[2-(4-Methyl-1,4-diazepan-1-yl)ethyl]-5-(4-nitrobenzoyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (24k) A solution of 1-[2-(4-methyl-1,4-diazepan-1-yl)-2-oxoethyl]-1,3,4,5-tetrahydro-1,5-benzodiazepin-2(2*H*)-one (22b) (430 mg) in THF (10 ml) was added to a suspension of LAH (220 mg) in THF (10 ml), and the mixture was stirred for 8 h at reflux temperature. After cooling, MeOH (2 ml) was added dropwise, and then this mixture was poured into water. It was extracted with $CHCl_3$. The organic layer was washed with brine, dried, and concentrated to give crude 1-[2-(4-methyl-1,4-diazepan-1-yl)ethyl]-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (**23b**) (320 mg) as a colorless oil. **12** (265 mg) was added to an ice-cooled solution of **23b** (320 mg) in THF (10 ml) at 0—5 °C, and the mixture was stirred for 18 h at room temperature. It was poured into saturated aqueous $NaHCO_3$, and the insoluble material was removed by filtration. The filtrate was extracted with AcOEt. The organic layer was washed with brine, dried, and concentrated. The residue was chromatographed over silica gel using 100 : 1 $CHCl_3$–MeOH to give **24k** (140 mg, 24%) as a yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.3—2.1 (3H, m), 2.40 (3H, s), 2.5—3.5 (16H, m), 4.4—4.7 (1H, m), 6.57 (2H, d), 6.9—7.2 (2H, m), 7.3—7.6 (2H, m), 7.98 (2H, d). FAB-MS m/z: 438 (M^++1).

In the same manner, compound **24l** was synthesized.

1-(4-Aminobenzoyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (25a) A mixture of **13** (1.0 g) and 10% Pd–C (100 mg) in AcOH (20 ml) was

Table 9. Physical and Spectral Data of 5-Substituted 1-(4-Nitrobenzoyl)-1,5-benzodiazepine Derivatives

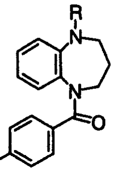


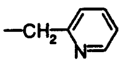
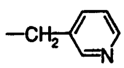
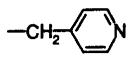
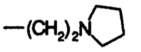
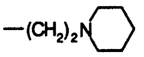
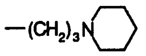
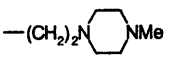
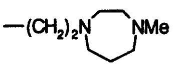
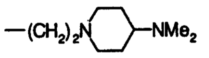
No.	R	Yield (%)[a]	mp (°C)	Formula[b]	^{1}H-NMR($CDCl_3$) δ	MS m/z (M^++1)
13	—H	87	160—162	$C_{16}H_{15}N_3O_3$	1.8—2.4 (2H, br), 2.7—3.3 (2H, br), 3.5—3.8 (1H, br), 4.9—5.2 (1H, m), 6.5—7.1 (4H, m), 7.42 (2H, d), 7.99 (2H, d)	298
14a	—Bzl	89	NT	NT	1.83 (1H, m), 2.06 (1H, m), 2.86 (1H, m), 3.15 (1H, m), 3.44 (1H, m), 4.28 (1H, d), 4.59 (1H, d), 4.70 (1H, m), 6.60 (2H, m), 7.0—7.5 (9H, m), 7.92 (2H, d)	388
14b	—CH_2CO_2Et	51	98—100	$C_{20}H_{21}N_3O_5$	1.32 (3H, t), 1.96 (1H, m), 2.16 (1H, m), 3.16 (2H, m), 3.62 (1H, m), 3.98 (1H, d), 4.16 (1H, d), 4,27 (2H, q), 4.72 (1H, m), 6.57 (2H, m), 6.76 (1H, d), 7.06 (1H, m), 7.48 (2H, d), 8.00 (2H, d)	384
14c	—CH_2CONH_2	47	154—156	$C_{18}H_{18}N_4O_4 \cdot 1/5H_2O$	1.92 (1H, br), 2.16 (1H, br), 2.99 (1H, br), 3.17 (1H, br), 3.44 (1H, br), 3.80 (1H, d), 4.07 (1H, d), 4.74 (1H, m), 5.64 (1H, m), 6.64 (1H, d), 6.73 (1H, t), 7.01 (1H, d), 7.19 (1H, t), 7.35 (2H, d), 8.01 (2H, d)	355
16	Ph	25	160—163	$C_{22}H_{19}N_3O_3$	1.7—2.3 (2H, br), 3.2—3.8 (4H, br), 6.4—7.5 (11H, m), 8.03 (2H, d)	374
24a		88	142—144	$C_{22}H_{20}N_4O_3$	1.90 (1H, m), 2.10 (1H, m), 3.00 (1H, m), 3.20 (1H, m), 3.50 (1H, m), 4.47 (1H, d), 4.70 (2H, m), 6.60 (2H, br), 7.0—7.5 (6H, m), 7.70 (1H, t), 7.90 (2H, d), 8.61 (1H, d)	389
24b		99	135—136	$C_{22}H_{20}N_4O_3 \cdot 1/4H_2O$	1.80 (1H, m), 2.10 (1H, m), 2.85 (1H, m), 3.15 (1H, m), 3.40 (1H, m), 4.29 (1H, d), 4.58 (1H, d), 4.70 (1H, m), 6.5—6.7 (2H, m), 7.0—7.3 (5H, m), 7.78 (1H, d), 7.93 (2H, d), 8.59 (1H, d), 8.69 (1H, s)	389
24c		99	NT	NT	1.87 (1H, br), 2.10 (1H, br), 2.89 (1H, br), 3.17 (1H, br), 3.40 (1H, br), 4.23 (1H, d), 4.59 (1H, d), 4.74 (1H, br), 6.34 (2H, m), 7.01 (1H, d), 7.13 (1H, m), 7.36 (4H, m), 7.97 (2H, d), 8.62 (2H, d)	389
24d	—$(CH_2)_2NMe_2$	51	NT	NT	1.55 (6H, s), 1.86 (1H, br), 2.08 (1H, br), 2.6—3.0 (4H, m), 3.25 (1H, m), 3.50 (1H, m), 4.60 (1H, br), 6.5—6.7 (2H, m), 7.0—7.3 (2H, m), 7.37 (2H, d), 8.02 (2H, d)	369
24e	—$(CH_2)_2NEt_2$	45	NT	NT	1.55 (6H, t), 1.8—1.9 (1H, br), 2.0—2.5 (6H, m), 3.0—4.0 (8H, m), 6.5—6.7 (2H, m), 7.3—7.5 (4H, m), 8.0—8.2 (2H, m)	396[c]
24f	—$(CH_2)_2N(isoPr)_2$	48	NT	NT	1.51 (12H, br), 1.86 (1H, br), 2.10 (1H, br), 2.4—3.3 (8H, m), 4.32 (1h, br), 4.60 (1H, br), 6.61 (1H, d), 6.72 (1H, m), 7.2—7.3 (4H, m), 7.99 (1H, d)	425
24g		95	NT	NT	1.64 (2H, br), 1.8—1.9 (4H, m), 2.09 (2H, br), 2.61 (4H, d), 2.7—2.9 (3H, m), 3.1—3.3 (2H, m), 3.4—3.5 (2H, m), 4.64 (1H, br), 6.55 (2H, m), 7.00 (1H, d), 7.10 (1H, m), 7.41 (2H, d), 7.96 (2H, d)	395
24h		77	NT	NT	1.45 (2H, br), 1.6—1.7 (4H, m), 1.87 (1H, br), 2.08 (1H, br), 2.49 (4H, br), 2.6—2.7 (2H, m), 2.88 (1H, m), 3.15 (1H, m), 3.29 (1H, m), 3.5—3.6 (2H, m), 4.66 (1H, m), 6.56 (2H, m), 7.00 (1H, d), 7.10 (1H, m), 7.41 (2H, d), 7.98 (2H, d)	409
24i		95	NT	NT	1.44 (2H, br), 1.59 (6H, m), 1.86 (3H, br), 2.08 (1H, br), 2.3—2.5 (4H, br), 2.83 (1H, m), 3.14 (2H, m), 3.38 (1H, m), 3.49 (1H, m), 4.63 (1H, m), 6.56 (2H, m), 6.97 (1H, d), 7.11 (1H, m), 7.37 (2H, d), 7.99 (2H, d)	423
24j		43	98—101	$C_{23}H_{29}N_5O_3 \cdot 1/5H_2O$	1.87 (1H, m), 2.08 (1H, m), 2.28 (3H, s), 2.4—2.7 (10H, m), 2.91 (1H, m), 3.16 (1H, m), 3.28 (1H, m), 3.54 (2H, m), 4.64 (1H, m), 6.56 (2H, m), 6.97 (1H, d), 7.11 (1H, m), 7.39 (2H, d), 7.97 (2H, d)	424
24k		24	NT	NT	1.3—2.1 (3H, m), 2.40 (3H, s), 2.5—3.5 (16H, m), 4.4—4.7 (1H, m), 6.57 (2H, d), 6.9—7.2 (2H, m), 7.3—7.6 (2H, m), 7.98 (2H, d)	438
24l		57	NT	NT	1.86 (2H, d), 2.0—2.2 (6H, m), 2.25 (6H, s), 2.63 (2H, m), 2.91 (1H, m), 3.04 (2H, m), 3.15 (1H, m), 3.26 (1H, m), 3.53 (2H, m), 4.63 (1H, m), 6.56 (2H, m), 6.97 (1H, d), 7.11 (1H, m), 7.39 (2H, d), 7.97 (2H, d)	452

a) Yields were based on the final step (**13**, **14**, **16**, **24a**—**j**) and the final two steps (**24k**, **24l**) of the synthetic method and were not optimized. *b*) See footnotes in Table 1. *c*) EI-MS (M^+). NT: not tested (oil).

stirred under a hydrogen atmosphere (1 atm) at room temperature. After absorption of 75 ml of hydrogen, the catalyst was removed by filtration, and the filtrate was concentrated. To the residue was added water, and the resulting solution was made basic with 1 N NaOH. The whole was extracted with AcOEt. The organic layer was washed with brine, dried, and concentrated. The residue was crystallized from AcOEt to give **25a** (850 mg, 95%) as a colorless powder, mp 190—192 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.67(1H, br), 1.94 (1H, br), 2.87 (1H, br), 3.00 (1H, br), 3.57 (1H, br), 3.72 (2H, br), 3.94 (1H, br), 5.07 (1H, br), 6.39 (2H, d), 6.5—6.7 (2H, m), 6.76 (1H, d), 6.9—7.0 (1H, m), 7.10 (2H, d). FAB-MS *m/z*: 268 (M^++1). *Anal.* Calcd for $C_{16}H_{17}N_3O \cdot 1/10H_2O$: C, 71.41; H, 6.44; N, 15.61. Found: C, 71.40; H, 6.55; N, 15.28.

Table 10. Physical and Spectral Data of 5-Substituted 1-(4-Aminobenzoyl)-1,5-benzodiazepine Derivatives



No.	R	Yield (%)[a)]	mp (°C)	Formula[b)]	^{1}H-NMR ($CDCl_3$) δ	MS m/z (M^++1)
25a	—H	94	190—192	$C_{16}H_{17}N_3O \cdot 1/10H_2O$	1.67 (1H, br), 1.94 (1H, br), 2.87 (1H, br), 3.00 (1H, br), 3.57 (1H, br), 3.72 (2H, br), 3.94 (1H, br), 5.07 (1H, br), 6.39 (2H, d), 6.5—6.7 (2H, m), 6.76 (1H, d), 6.9—7.0 (1H, m), 7.10 (2H, d)	268
25b	—Ph	74	236—240	$C_{22}H_{21}N_3O$	1.4—1.7 (2H, br), 1.8—2.2 (2H, br), 3.5—4.0 (4H, br), 6.44 (2H, d), 6.7—7.4 (11H, m)	344
25c	—Bzl	84	159—160	$C_{23}H_{23}N_3O_1$	1.78 (1H, br), 1.98 (1H, br), 2.81 (1H, br), 3.12 (1H, br), 3.41 (1H, br), 4.12 (1H, d), 4.57 (1H, d), 4.66 (1H, br), 6.41 (2H, d), 6.66 (2H, br), 7.02 (1H, d), 7.1—7.2 (3H, m), 7.3—7.4 (3H, m), 7.42 (2H, d)	358
25d		76	121—123	$C_{22}H_{22}N_4O$	1.86 (1H, br), 2.05 (1H, br), 2.95 (1H, br), 3.17 (1H, br), 3.49 (1H, br), 4.47 (1H, d), 4.69 (2H, m), 6.35 (2H, d), 6.65 (2H, m), 7.0—7.3 (5H, m), 7.53 (1H, d), 7.65 (1H, m), 8.58 (1H, m)	359
25e		64	161—163	$C_{22}H_{22}N_4O \cdot 1/5H_2O$	1.78 (1H, br), 1.97 (1H, br), 2.82 (1H, br), 3.14 (1H, br), 3.36 (1H, br), 4.30 (1H, d), 4.55 (2H, m), 6.34 (2H, d), 6.70 (2H, s), 7.0—7.3 (5H, m), 7.79 (1H, d), 8.54 (1H, br), 8.65 (1H, br)	359
25f		83	186—189	$C_{22}H_{22}N_4O \cdot 1/5H_2O$	1.83 (1H, br), 2.03 (1H, br), 2.87 (1H, br), 3.16 (1H, br), 3.41 (1H, br), 4.30 (1H, d), 4.57 (1H, d), 4.68 (1H, br), 6.35 (2H, d), 6.69 (2H, d), 7.0—7.1 (3H, m), 7.36 (2H, d), 8.56 (2H, d)	359
25g	$—CH_2CONH_2$	49	NT	NT	1.83 (1H, br), 2.04 (1H, br), 2.90 (1H, br), 3.13 (1H, br), 3.38 (1H, br), 3.80 (1H, br), 4.05 (1H, br), 4.68 (1H, br), 5.54 (1H, br), 6.4—7.2 (8H, m)	325
25k		87	159—162	$C_{22}H_{28}N_4O \cdot 1/5H_2O$	1.64 (1H, br), 1.79 (6H, br), 2.02 (1H, br), 2.60 (3H, br), 2.90 (1H, br), 3.16 (1H, br), 3.29 (1H, br), 3.55 (1H, br), 3.70 (2H, s), 4.58 (1H, br), 6.38 (2H, d), 6.60 (2H, m), 6.96 (2H, d), 7.11 (3H, m)	365
25l		86	170—173	$C_{23}H_{30}N_4O \cdot 1/5H_2O$	1.44 (2H, br), 1.59 (6H, s), 1.82 (1H, br), 2.02 (1H, br), 2.48 (3H, br), 2.89 (1H, br), 3.16 (1H, br), 3.30 (1H, br), 3.51 (2H, br), 3.69 (1H, br), 4.59 (1H, br), 6.38 (2H, d), 6.60 (2H, d), 6.96 (2H, d), 7.07 (3H, m)	379
25m		64	110—115	$C_{24}H_{32}N_4O \cdot 1/4H_2O$	1.43 (2H, br), 1.59 (4H, m), 1.8—2.0 (2H, br), 2.01 (1H, br), 2.37 (6H, br), 2.82 (1H, br), 3.14 (1H, br), 3.35 (1H, br), 3.48 (1H, br), 3.70 (2H, s), 4.57 (1H, br), 6.38 (2H, d), 6.61 (2H, d), 6.95 (2H, d), 7.07 (3H, m)	393
25n		Quant.	NT	NT	1.64 (4H, s), 1.82 (1H, br), 2.03 (1H, br), 2.28 (3H, s), 2.4—2.7 (5H, m), 2.89 (1H, br), 3.17 (1H, br),3.29 (1H, br), 3.54 (2H, br), 3.71 (1H, br), 4.59 (1H, br), 6.38 (2H, d), 6.61 (2H, d), 6.95 (2H, d), 7.07 (3H, m)	394
25o		75	NT	NT	1.7—2.1 (4H, m), 2.35 (3H, s), 2.5—3.0 (11H, m), 3.2—4.9 (4H, m), 4.4—4.7 (1H, br), 6.37 (2H, d), 6.5—6.7 (2H, m), 7.0—7.2 (4H, m)	408
25p		60	NT	NT	1.56 (4H, m), 1.80 (2H, d), 2.0—2.2 (4H, m), 2.27 (6H, s), 2.61 (2H, t), 2.89 (1H, br), 3.03 (2H, d), 3.16 (1H, br), 3.29 (1H, br), 3.54 (1H, br), 3.71 (1H, s), 4.59 (1H, br), 6.38 (2H, d), 6.61 (2H, d), 6.95 (2H, d), 7.07 (3H, m)	422
25q	$—CH_2CO_2Et$	98	158—161	$C_{20}H_{23}N_3O_3 \cdot 1/10H_2O$	1.30 (3H, t), 1.95 (1H, br), 2.08 (1H, br), 3.17 (2H, br), 3.66 (1H, br), 4.0—4.2 (2H, m), 4.11 (2H, q), 4.68 (1H, br), 6.5—6.6 (4H, m), 6.78 (1H, d), 7.04 (1H, m), 7.23 (2H, d)	354

a, b) See footnotes in Table 1. NT: not tested ((oil).

In the same manner, compounds **25b**, **25g**, and **25k**—**q** were synthesized.

1-(4-Aminobenzoyl)-5-benzyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (25c) $SnCl_2 \cdot 2H_2O$ (1.05 g) was added to a solution of **14a** (300 mg) in AcOEt (10 ml), and the mixture was stirred for 1.5 h at reflux temperature. After cooling, saturated aqueous $NaHCO_3$ and AcOEt were added to the mixture. Insoluble material was removed by filtration. The filtrate was extracted with AcOEt. The organic layer was washed with brine, dried, and concentrated. The residue was crystallized from Et_2O to give **25c** (230 mg, 84%) as a colorless powder, mp 159—160 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.78 (1H, br), 1.98 (1H, br), 2.81 (1H, br), 3.12 (1H, br), 3.41 (1H, br), 4.12 (1H, d), 4.57 (1H, d), 4.66 (1H, br), 6.41 (2H, d), 6.66 (2H, br), 7.02 (1H, d), 7.1—7.2 (3H, m), 7.3—7.4 (3H, m), 7.42 (2H, d). FAB-MS m/z: 358 (M^++1). *Anal.* Calcd for $C_{23}H_{23}N_3O$: C, 77.28; H, 6.49; N, 11.76. Found: C, 77.20; H, 6.65; N, 11.57.

In the same manner, compounds **25d**—**f** were synthesized.

2-Phenyl-4′-(2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-carbonyl)benzanilide (26a) A mixture of **25a** (4.5 g), **2a** (3.3 g), WSC (3.9 g), and HOBt (2.7 g) in DMF (50 ml) was stirred for 5 d at room temperature. It was poured into water, and the whole was extracted with AcOEt. The organic layer was washed with 1 N HCl, 1 N NaOH, and brine, dried and concentrated. The residue was collected by filtration and washed with AcOEt to give **26a** (3.2 g, 42%) as a colorless powder, mp 219—223 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.94 (1H, br), 2.05 (1H, br), 2.86 (1H, br), 2.96 (1H, br), 3.55 (1H, br), 3.93 (1H, br), 5.03 (1H, br), 6.52 (2H, m), 6.7—7.0 (5H, m), 7.12 (2H, d), 7.3—7.6 (7H, m), 7.84 (1H, d). FAB-MS m/z: 448 (M^++1). *Anal.* Calcd for $C_{29}H_{25}N_3O_2 \cdot 1/5H_2O$: C, 77.21; H, 5.67; N, 9.31. Found: C, 77.12; H, 5.74; N, 9.23.

In the same manner, compound **26b** was synthesized.

4′-(5-Acetyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-carbonyl)-2-phenylbenzanilide (27a) Acetic anhydride (50 ml) was added to a solution of **26a** (220 mg) in pyridine (5 ml), and the mixture was stirred for 12 h at 70 °C. It was poured into AcOEt, and the whole was washed with saturated aqueous $NaHCO_3$ and brine, dried, and concentrated. The residue was crystallized from Et_2O to give **27a** (150 mg, 61%) as a colorless amorphous solid. ^{1}H-NMR ($CDCl_3$) δ: 1.70 (1H, br), 2.02 (3H, s), 2.09 (1H, br), 2.83 (1H, br), 2.97 (1H, br), 4.73 (1H, br), 6.8—7.6 (16H, m), 7.86 (1H, d). FAB-MS *m/z*: 490 (M^++1). *Anal.* Calcd for $C_{31}H_{27}N_3O_3 \cdot 1/2H_2O$: C, 74.68; H, 5.66; N, 8.43. Found: C, 74.68; H, 5.83; N, 8.11.

4′-(5-Benzoyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-carbonyl)-2-phenylbenzanilide (27b) Benzoyl chloride (60 ml) was added to a solution of **26a** (220 mg) and Et_3N (70 ml) in CH_2Cl_2 (10 ml), and the mixture was stirred for 2 h at room temperature. It was washed with saturated aqueous $NaHCO_3$ and brine, dried, and concentrated. The residue was chromatographed over silica gel using 50 : 1 $CHCl_3$–MeOH and crystallized from Et_2O to give **27b** (220 mg, 80%) as a colorless powder, mp 150—155 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.7—2.1 (2H, br), 2.8—3.3 (3H, br), 4.6—4.9 (1H, br), 6.8—7.7 (21H, m), 7.88 (1H, d). FAB-MS *m/z*: 552 (M^++1). *Anal.* Calcd for $C_{36}H_{29}N_3O_3 \cdot H_2O$: C, 75.90; H, 5.48; N, 7.38. Found: C, 75.56; H, 5.31; N, 7.16.

4′-(5-Methyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-carbonyl)-2-phenylbenzanilide (28) To an ice-cooled solution of **2a** (95 mg) in CH_2Cl_2 (10 ml) were added catalytic DMF and oxalyl chloride (120 mg) at 0—5 °C, and the mixture was stirred for 30 min at this temperature. It was concentrated and the residue was dissolved in CH_2Cl_2 (10 ml). The solution was added dropwise to an ice-cooled solution of 1-(4-aminobenzoyl)-5-methyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine[4] (110 mg) and Et_3N (40 mg) in CH_2Cl_2 (10 ml), and the mixture was stirred for 18 h at room temperature. It was washed with saturated aqueous $NaHCO_3$ and brine, dried, and concentrated. The residue was chromatographed over silica gel using $CHCl_3$ and crystallized from EtOH to give **28** (80 mg, 43%) as a colorless powder, mp 202—207 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.82 (1H, br), 2.05 (1H, br), 2.82 (1H, br), 2.92 (3H, s), 3.10 (1H, br), 3.44 (1H, br), 4.61 (1H, br), 6.5—6.6 (2H, m), 6.8—7.0 (4H, m), 7.0—7.1 (3H, m), 7.3—7.6 (8H, m), 7.83 (1H, d). FAB-MS *m/z*: 462(M^++1). *Anal.* Calcd for $C_{30}H_{27}N_3O_2 \cdot 1/5H_2O$: C, 77.46; H, 5.94; N, 9.03. Found: C, 77.62; H, 5.95; N, 8.98.

In the same manner, compounds **29**, **30**, **31a—c**, **32a**, and **33d—i** were synthesized.

4′-[5-(2-Dimethylaminoethyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-carbonyl]-2-phenylbenzanilide Monohydrochloride (33a) A mixture of 1-(2-dimethylaminoethyl)-5-(4-nitrobenzoyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (**24d**) (510 mg) and 10% Pd–C (500 mg) in MeOH (10 ml) was stirred under a hydrogen atmosphere (1 atm) at room temperature. After absorption of 93 ml of hydrogen, the catalyst was removed by filtration, and the filtrate was concentrated to give crude 1-(4-aminobenzoyl)-5-(2-dimethyaminoethyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (**25h**) (547 mg) as a yellow oil. To an ice-cooled solution of **2a** (385 mg) in CH_2Cl_2 (10 ml) were added catalytic DMF and oxalyl chloride (340 μl) at 0—5 °C, and the mixture was stirred for 30 min at this temperature. It was concentrated and the residue was dissolved in CH_2Cl_2 (10 ml). The solution was added dropwise to a solution of **25h** (547 mg) and Et_3N (270 μl) in CH_2Cl_2 (10 ml) at 0—5 °C, and the mixture was stirred for 5 h at room temperature. It 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 residue (414 mg) was dissolved in AcOEt, and to the solution was added a solution of 4 N HCl in AcOEt (250 μl) at 0—5 °C. The resulting precipitate was filtered and recrystallized from MeOH–AcOEt to give **33a** (290 mg, 35%) as a colorless powder, mp 153—156 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.68 (1H, br), 1.96 (1H, br), 2.81 (6H, s), 3.01 (1H, br), 3.33 (1H, br), 3.55 (4H, m), 3.77 (1H, br), 4.42 (1H, br), 6.6—7.6 (18H, m). FAB-MS *m/z*: 519 (M^++1). *Anal.* Calcd for $C_{33}H_{34}N_4O_2 \cdot 3/2HCl \cdot 3/2H_2O$: C, 66.02; H, 6.46; N, 9.33; Cl, 8.86. Found: C, 65.55; H, 6.42; N, 9.16; Cl, 9.23.

In the same manner, compounds **33b** and **33c** were synthesized.

Ethyl {5-[4-(2-Phenylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-1-yl}acetate (34) To an ice-cooled solution of **2a** (42 g) in CH_2Cl_2 (300 ml) were added catalytic DMF and oxalyl chloride (41 g) at 0—5 °C, and the mixture was stirred for 30 min at this temperature. It was concentrated and the residue was dissolved in CH_2Cl_2 (150 ml). The solution was added dropwise to an ice-cooled solution of ethyl [5-(4-aminobenzoyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-1-yl]acetate (**25q**) (63 g) and Et_3N (34 g) in CH_2Cl_2 (1000 ml), and the mixture was stirred for 30 min at room temperature. It was washed with saturated aqueous $NaHCO_3$ and brine, dried, and concentrated. The residue was recrystallized from AcOEt to give **34** (70 g, 74%) as a colorless powder, mp 175—177 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, t), 1.94 (1H, br), 2.08 (1H, br), 3.15 (2H, br), 3.63 (1H, br), 3.98 (1H, d), 4.09 (1H, br), 4.25 (2H, q), 4.67 (1H, br), 6.54 (2H, br), 6.72 (1H, d), 6.9—7.6 (13H, m), 7.81 (1H, d). FAB-MS *m/z*: 534 (M^++1). *Anal.* Calcd for $C_{33}H_{31}N_3O_4$: C, 74.28; H, 5.86; N, 7.87. Found: C, 74.30; H, 5.99; N, 7.80.

{5-[4-(2-Phenylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-1-yl}acetic Acid (35) A mixture of **34** (76 g) and 1 N NaOH (300 ml) in THF (1.5 l) was stirred for 18 h at room temperature. It was concentrated, and to the residue was added 1 N HCl (300 ml). The resulting precipitate was collected by filtration and washed with water to give **35** (68.3 g, 94%) as a colorless powder, mp 202—205 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.79 (1H, br), 1.96 (1H, br), 3.04 (2H, br), 3.57 (1H, br), 4.00 (1H, d), 4.14 (1H, d), 4.67 (1H, br), 6.54 (2H, s), 6.78 (1H, d), 7.0—7.6 (14H, m), 10.26 (1H, s), 12.68 (1H, br). FAB-MS *m/z*: 506 (M^++1). *Anal.* Calcd for $C_{31}H_{27}N_3O_4$: C, 73.65; H, 5.38; N, 8.31. Found: C, 73.62; H, 5.47; N, 8.26.

***N*-Methyl-{5-[4-(2-Phenylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-1-yl}acetamide (32b)** A 40% solution of methylamine in MeOH (14 ml) was added to a solution of **35** (18.2 g), WSC (8.28 g), and HOBt (5.84 g) in THF (1.5 l), and the mixture was stirred for 3 h at room temperature. It was concentrated, and to the residue was added 1 N NaOH. The whole was extracted with $CHCl_3$. The organic layer was washed with brine, dried, and concentrated. The residue was crystallized from AcOEt, then recrystallized from EtOH to give **32b** (12.51 g, 67%) as a colorless powder, mp 160—165 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.84 (1H, br), 2.08 (1H, br), 2.81 (3H, s), 2.89 (1H, br), 3.13 (1H, br), 3.35 (1H, br), 3.74 (1H, d), 4.04 (1H, d), 4.69 (1H, br), 6.6—7.6 (16H, m), 7.85 (1H, d). FAB-MS *m/z*: 519 (M^++1). *Anal.* Calcd for $C_{32}H_{30}N_4O_3 \cdot 3/2H_2O$: C, 70.44; H, 6.10; N, 10.27. Found: C, 70.47; H, 6.06; N, 10.76.

In the same manner, compounds **32c—j** were synthesized.

Receptor Binding Assay[17] Plasma membrane preparations were incubated with various concentrations of [^{3}H]AVP or [^{3}H]OT (0.1—3.0 nM). Radioligands (0.5 nM) were added to each membrane preparation and the mixture was incubated with various concentrations of the compounds in 250 μl of assay buffer (50 mM Tris–HCl, pH 7.5, 5 mM $MgCl_2$, and 0.1% bovine serum albumin). After incubation (60 min at 25 °C), the reaction was terminated by the addition of 3 ml of ice-cooled Tris buffer (50 mM Tris–HCl, pH 7.5, and 5 mM $MgCl_2$), followed immediately by filtration using glass filters. The filters were rinsed twice with Tris buffer and the radioactivity retained on them was counted with a liquid scintillation counter. Specific binding was calculated as the total binding minus nonspecific binding, which was determined using 1 μM unlabeled AVP or OT. The concentration of test compound that caused 50% inhibition (IC_{50}) of the specific binding of [^{3}H]AVP or [^{3}H]OT was determined by regression analysis of displacement curves. The inhibitory dissociation constant (K_i) was calculated from the following formula: $K_i = IC_{50}/(1+[L]/K_d)$, where [L] is the concentration of radioligand present in the tubes and K_d is the dissociation constant of radioligand obtained from the Scatchard plot.

V_{1A} Receptor Antagonist Activity[17] Pithed rats were maintained at 37 °C by means of a thermostat-controlled heating board. For i.v. injection, compounds were dissolved in DMF. After stabilization of the blood pressure, compounds or vehicle was given (0.5 ml/kg, i.v.) 5 min before the injection of AVP (30 mU/kg, i.v.). The dose of compound causing a 50% inhibition of the pressor response to AVP (ID_{50}) was calculated.

V_2 Receptor Antagonist Activity[17] Rats were deprived of drinking water for 16—20 h to stimulate endogenous AVP secretion. For i.v. injection, compounds were dissolved in DMF and then diluted with water. Compounds or vehicle was administered intravenously and spontaneously voided urine was collected for a 2 h period. The dose causing an increase in urine volume by 3 ml after compound dosing (ED_3) was determined.

Oral Abilability[17] Rats were deprived of drinking water for 16—20 h to stimulate endogenous AVP secretion. Compounds were suspended in a 0.5% methyl cellulose solution. Compounds or vehicle was administered orally and spontaneously voided urine was collected for a 2 h period.

Acknowledgments We are grateful to the staff of the Division of Molecular Chemistry Research for elemental analysis and spectral measurements.

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