Preparation of Non-peptide, Highly Potent and Selective Antagonists of Arginine Vasopressin V_{1A} Receptor by Introduction of Alkoxy Groups

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A series of compounds structurally related to 4′-[(4,4-difluoro-5-methylidene-2,3,4,5-tetrahydro-1*H*-1-benzoazepin-1-yl)carbonyl]benzanilide were synthesized and evaluated for arginine vasopressin (AVP) antagonistic activity. Compounds with alkoxy groups (especially ethoxy group) at the 2′-position of benzanilide possessed potent affinity and selectivity for the V_{1A} receptor *versus* V_2 receptor. Further study has shown that the introduction of 4,4-dimethylaminopiperidino and morpholino groups at carbonylmethylene exhibited more potent affinity and selectivity for V_{1A} receptors. Consequently, we found that the (*Z*)-4′-({4,4-Difluoro-5-[(4-dimethylaminopiperidino)carbonylmethylene]-2,3,4,5-tetrahydro-1*H*-1-benzoazepin-1-yl}carbonyl)-2-ethoxybenzanilide monohydrochloride (8d) and the (*Z*)-4′-[(4,4-Difluoro-5-morpholinocarbamoylethylene-2,3,4,5-tetrahydro-1*H*-1-benzoazepin-1-yl)carbonyl]-2-ethoxybenzanilide (8q) exhibited potent and selective V_{1A} receptor antagonist activity. The synthesis and pharmacological properties of these compounds are detailed in this paper.

Key words arginine vasopressin antagonist; V_{1A} receptor selective; alkoxy group

Arginine vasopressin (AVP) is a nonapeptide secreted by the posterior pituitary gland. AVP is known as an anti-diuretic hormone (ADH) and demonstrates potent anti-diuretic and vasoconstrictor activities. The subtypes of the AVP receptor have been identified as V_{1A}, V_{1B} and V_2 in the periphery.[1—3] Among these receptors, the V_{1A} receptor is found in vascular smooth muscle, liver, platelets and renal mesangial cells. The V_2 receptor is found only in the kidney.

Considering the physiological properties of AVP, abnormal secretion of AVP is thought to be associated with high blood pressure, cardiac disease, kidney disease and hypernatremia.[4] Compounds which act as antagonists of AVP receptors are therefore expected to be highly effective drugs for the treatment of these conditions.

To this end, we have conducted initial investigations into the discovery of non-peptide antagonists of both V_{1A} and V_2 receptors. In the course of investigations of AVP antagonists, we have discovered and reported several compounds that exhibited similar highly potent affinity for these receptor subtypes.[5—7] In particular, 4′-(2-methyl-1,4,5,6-tetrahydroimidazo[4,5-*d*][1]-benzoazepine-6-carbonyl)-2-phenyl-benzanilide monohydrochloride (**1**, YM087) and (*Z*)-4′-({4,4-difluoro-5-[(4-dimethylaminopiperidino)carbonylmethylene]-2,3,4,5-tetrahydro-1*H*-1-benzoazepin-1-yl}carbonyl)-2-phenylbenzanilide monohydrochloride (**2**, YM-35471) possessed high binding affinities for both V_{1A} and V_2 receptors and potent AVP antagonist activity (Fig. 1).[8,9]

Considering that subtype selective AVP receptor antagonists may be useful for investigation of the pathophysiological roles of AVP and could lead to new therapeutic tools, we then decided to study selective non-peptide antagonists of the V_{1A} receptor as a next target.

Selective non-peptide antagonists of the V_{1A} receptor reported to date include OPC-21268 (**3**)[10] and SR49059 (**4**)[11] (Fig. 2). We had already discovered compounds possessing high binding affinities for both V_{1A} and V_2 receptors as described above, and chose **2** as the lead compound because it showed the most potent V_{1A} receptor binding affinity among our compounds. On modification of **2**, we presumed that modification of biphenyl moiety, shown in the box in Fig. 3, would show V_{1A} selectivity versus V_2 receptor on the basis of our investigations of AVP antagonists.[5,8]

Therefore, we first modified R_1 and R_2 positions of **2**, then optimized the R_3 position.

In this paper, we described the SAR within a series of these derivatives that led to the discovery of a highly potent and selective V_{1A} receptor antagonist.

Chemistry The synthesis pathways of the compounds listed in Table 1—4 are shown in Chart 1. The methyl ester derivatives (**6a**—**h**) were obtained by reacting substituted benzoyl chloride with methyl (*Z*)-[4,4-difluoro-1-(4-aminobenzoyl)-2,3,4,5-tetrahydro-1*H*-1-benzoazepin-5-ylidene] acetate (**5**).[9] Each derivative was hydrolyzed to acetic acid derivative (**7a**—**h**) under basic condition. Condensation of **7** and various amines in the presence of 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (WSC.HCl) and 1-hydroxybenzotriazole (HOBt) gave the target amide derivatives (**2**, **8b**—**r**).

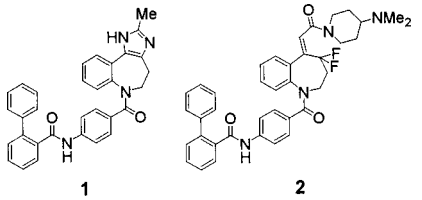

Fig. 1

Results and Discussion

Binding Affinities Methods for determining the *in vitro* AVP receptor binding affinities are described in Experimental. The results of the binding assay of compounds are shown in Tables 3 and 4.

Initially, we investigated the influence of various substituent groups at the R_1 and R_2 position of 4-(*N*,*N*-dimethylamino) piperidine derivatives, as shown in Table 3. The

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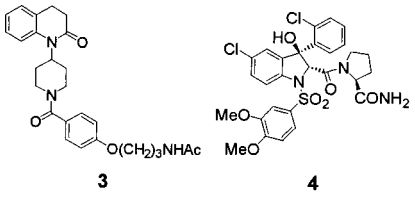


Fig. 2

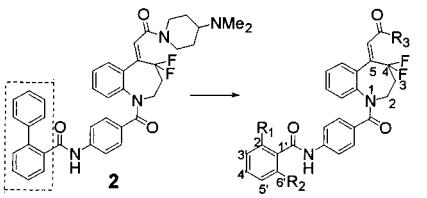


Fig. 3

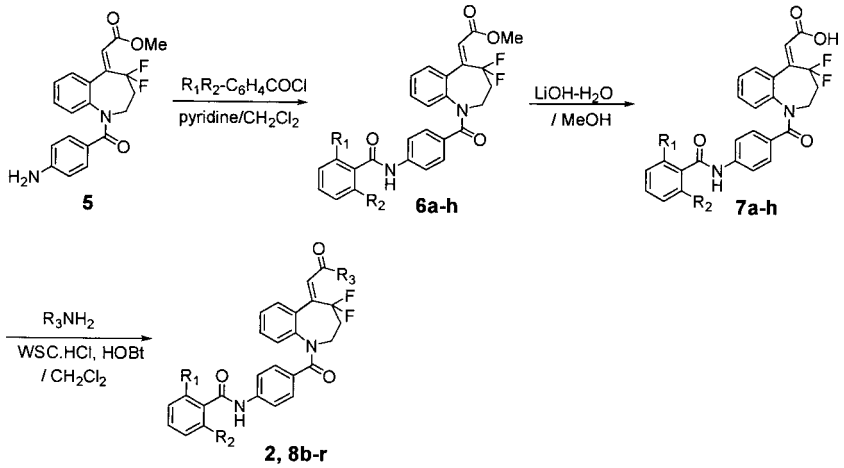
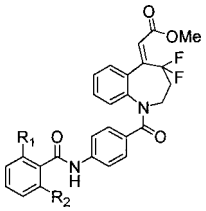


Chart 1

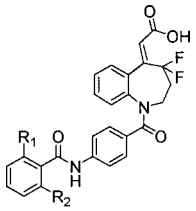
Table 1. Physical and Spectral Data of Methyl Ester Derivatives



No.	R_1	R_2	Yield (%)	^{1}H-NMR ($CDCl_3$) δ	FAB-MS *m/z* (M^++1)
6a	Ph	H	95	2.30—2.80 (2H, m), 3.21 (1H, m), 3.83 (3H, s), 5.03 (1H, m), 6.17 (1H, s), 6.66 (1H, m), 6.91 (3H, m), 7.01 (2H, m), 7.09 (1H, t, *J*=7 Hz), 7.24 (1H, t, *J*=8 Hz), 7.33—7.49 (8H, m), 7.50—7.60 (1H, m), 7.83 (1H, d, *J*=7 Hz)	552[b]
6b	Me	H	98	2.02—2.82 (2H, m), 2.47 (3H, s), 3.21 (1H, m), 3.83 (3H, s), 5.06 (1H, m), 6.21 (1H, s), 6.73 (1H, d, *J*=8 Hz), 7.12—7.50 (12H, m)	490[b]
6c	OMe	H	95	2.26—2.84 (2H, m), 3.26 (1H, m), 3.83 (3H, s), 4.03 (3H, s), 5.03 (1H, m), 6.21 (1H, s), 6.73 (1H, m), 7.02 (1H, d, *J*=7 Hz), 7.09—7.28 (5H, m), 7.37 (1H, d, *J*=8 Hz), 7.50 (3H, m), 8.23 (1H, m), 9.84 (1H, m)	506[b]
6d	OEt	H	99	1.61 (3H, t, *J*=7 Hz), 2.32—2.82 (2H, m), 3.24 (1H, m), 3.84 (3H, s), 4.26 (2H, q, *J*=7 Hz), 5.03 (1H, m), 6.22 (1H, s), 6.73 (1H, m), 7.02 (1H, d, *J*=7 Hz), 7.06—7.18 (4H, m), 7.24 (1H, t, *J*=8 Hz), 7.37 (1H, d, *J*=8 Hz), 7.47 (3H, m), 8.24 (1H, m), 10.12 (1H, m)	520[b]
6e	O-*i*-Pr	H	97	1.50 (6H, d, *J*=6 Hz), 2.35—2.82 (2H, m), 3.23 (1H, m), 3.84 (3H, s), 4.82 (1H, m), 5.07 (1H, m), 6.22 (1H, s), 6.73 (1H, m), 7.00 (1H, d, *J*=7 Hz), 7.08—7.18 (4H, m), 7.24 (1H, t, *J*=8 Hz), 7.38 (1H, d, *J*=8 Hz), 7.47 (3H, m), 8.24 (1H, m), 10.25 (1H, m)	535
6f	Cl	H	99	2.27—2.82 (2H, m), 3.26 (1H, m), 3.83 (3H, s), 5.04 (1H, m), 6.21 (1H, s), 6.73 (1H, m), 7.10—7.20 (3H, m), 7.26 (1H, t, *J*=8 Hz), 7.34—7.50 (6H, m), 7.72 (1H, d, *J*=8 Hz), 7.98 (1H, s)	510, 512[b]
6g	NO_2	H	89	2.25—2.82 (2H, m), 3.24 (1H, m), 3.83 (3H, s), 5.04 (1H, m), 6.24 (1H, s), 6.75 (1H, m), 7.10—7.20 (3H, m), 7.14 (1H, t, *J*=8 Hz), 7.38 (1H, m), 7.52 (2H, d, *J*=8 Hz), 7.57—7.67 (2H, m), 7.72 (1H, t, *J*=7 Hz), 8.08 (1H, d, *J*=7 Hz), 10.09 (1H, s)[a]	522
6h	OMe	OMe	94	2.30—2.80 (2H, m), 3.24 (1H, m), 3.81 (6H, s), 3.83 (3H, s), 5.07 (1H, m), 6.20 (1H, s), 6.58 (2H, d, *J*=8 Hz), 6.74 (1H, d, *J*=8 Hz), 7.11—7.18 (3H, m), 7.26 (1H, d, *J*=7 Hz), 7.31 (1H, t, *J*=7 Hz), 7.38 (1H, d, *J*=7 Hz), 7.40—7.52 (4H, m)	537

a) ^{1}H-NMR spectra were measured in DMSO-d_6. *b*) EI-MS (M^+).

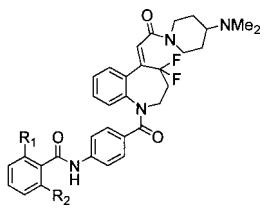
Table 2. Physical and Spectral Data of Acetic Acid Derivatives



No.	R_1	R_2	Yield (%)	^{1}H-NMR ($CDCl_3$) δ	FAB-MS *m/z* ($M^+ + 1$)
7a	Ph	H	76	2.41 (1H, m), 2.67 (1H, m), 3.24 (1H, m), 3.68 (1H, m), 5.00 (1H, m), 6.19 (1H, s), 6.67 (1H, m), 6.92 (2H, m), 6.98 (3H, m), 7.10 (1H, t, *J*=8 Hz), 7.24 (1H, d, *J*=7 Hz), 7.30—7.50 (8H, m), 7.53 (1H, m), 7.80 (1H, d, *J*=8 Hz)	538[c]
7b	Me	H	90	2.15—3.00 (2H, m), 2.43 (3H, s), 3.35 (1H, m), 5.02 (1H, m), 6.20 (1H, s), 6.75 (1H, m), 7.08—7.49 (12H, m), 7.67 (1H, br)	476[c]
7c	OMe	H	89	2.20—2.80 (2H, m), 3.26 (1H, m), 4.03 (3H, s), 5.03 (1H, m), 6.21 (1H, s), 6.73 (1H, m), 7.02 (1H, d, *J*=7 Hz), 7.09—7.28 (5H, m), 7.37 (1H, d, *J*=8 Hz), 7.50 (3H, m), 8.23 (1H, m), 9.84 (1H, m)	492[c]
7d	OEt	H	99	1.59 (3H, t, *J*=7 Hz), 2.28—2.90 (2H, m), 3.28 (1H, m), 4.22 (2H, q, *J*=7 Hz), 5.03 (1H, m), 6.27 (1H, s), 6.73 (1H, m), 6.93 (1H, d, *J*=8 Hz), 7.06—7.18 (4H, m), 7.24 (1H, t, *J*=8 Hz), 7.26—7.30 (4H, m), 8.22 (1H, d, *J*=7 Hz), 10.16 (1H, m)	507
7e	O-*i*-Pr	H	75	1.47 (6H, d, *J*=6 Hz), 2.28—2.86 (2H, m), 3.28 (1H, m), 4.79 (1H, m), 5.07 (1H, m), 6.27 (1H, s), 6.73 (1H, m), 6.98 (1H, d, *J*=8 Hz), 7.06—7.20 (4H, m), 7.24 (1H, t, *J*=8 Hz), 7.39 (1H, d, *J*=8 Hz), 7.41—7.50 (4H, m), 8.21 (1H, m), 10.26 (1H, m)	521
7f	Cl	H	90	2.15—2.82 (2H, m), 3.22 (1H, m), 5.03 (1H, m), 6.24 (1H, s), 6.72 (1H, m), 7.09—7.20 (3H, m), 7.25 (1H, t, *J*=8 Hz), 7.32—7.48 (4H, m), 7.50—7.65 (3H, m), 9.85 (1H, s)[a]	497, 499
7g	NO_2	H	55	2.46 (2H, m), 3.11 (1H, m), 4.88 (1H, m), 6.68 (1H, s), 6.84 (1H, m), 7.09 (2H, d, *J*=8 Hz), 7.21 (1H, t, *J*=8 Hz), 7.31 (1H, t, *J*=8 Hz), 7.38 (1H, d, *J*=8 Hz), 7.50 (2H, d, *J*=7 Hz), 7.74—7.80 (2H, m), 7.86 (1H, t, *J*=7 Hz), 8.14 (1H, d, *J*=7 Hz), 10.74 (1H, s), 13.18 (1H, br)[a]	508
7h	OMe	OMe	88	2.50 (2H, m), 3.10 (1H, m), 3.73 (6H, s), 4.89 (1H, m), 6.66 (1H, s), 6.71 (2H, d, *J*=8 Hz), 6.83 (1H, m), 7.04 (2H, d, *J*=8 Hz), 7.20 (1H, t, *J*=8 Hz), 7.26—7.41 (3H, m), 7.52 (2H, d, *J*=7 Hz), 10.30 (1H, s), 13.21 (1H, m)[a]	523

a) ^{1}H-NMR spectra were measured in DMSO-d_6. *b*) EI-MS (M^+).

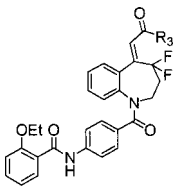
Table 3. Receptor-Binding Affinities for 4-(*N*,*N*-dimethylamino)piperidine Derivatives



No.	R_1	R_2	Binding affinity (pK_i)		V_{1A}/V_2[c]
			V_{1A}[a]	V_2[b]	
2	Ph	H	10.1	9.38	5
8b	Me	H	8.76	8.12	4
8c	OMe	H	8.89	7.62	19
8d	OEt	H	9.22	7.65	37
8e	O-*i*-Pr	H	9.19	8.10	12
8f	Cl	H	8.99	7.67	21
8g	NO_2	H	8.78	7.44	22
8h	OMe	OMe	8.08	6.30	60

a) pK_i of [^{3}H]vasopressin binding to rat liver membranes. *b*) pK_i of [^{3}H]vasopressin binding to rat kidney membranes. *c*) V_{1A}/V_2 showed the selectivity of binding affinity for V_{1A} versus V_2 receptor.

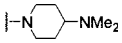
Table 4. Receptor-Binding Affinities for 2-Ethoxybenzanilide Derivatives



No.	R_3	Binding affinity (pK_i)		V_{1A}/V_2[c]
		V_{1A}[a]	V_2[b]	
8d		9.22	7.65	37
8i	NH_2	8.81	7.86	9
8j	NHMe	9.26	8.18	12
8k	NHEt	9.04	8.29	6
8l	NH-*n*-Pr	8.95	8.11	7
8m	NH-*i*-Pr	9.20	8.21	10
8n	NH-*c*-Pr	9.39	8.14	18
8o	NMe_2	8.95	8.28	5
8p	NEt_2	8.59	7.83	6
8q		9.80	8.19	41
8r		8.75	8.28	3

a—*c*) See footnotes for Table 3.

Table 5. Binding Affinities of Cloned Human V_{1A} (hV_{1A}) and V_2 (hV_2) Receptors and AVP-Antagonist Activities

No.	R_3	Binding affinity (pK_i)		V_{1A}/V_2 [c]	Antagonist activities V_{1A} [d] ID_{50} (mg/kg)
		hV_{1A} [a]	hV_2 [b]		
8d		9.05	7.34	51	0.0091
8q		9.80	8.15	44	0.019
YM087[8]		8.37	8.72	0.45	0.013

a—*c*) See footnotes for Table 3. *d*) ID_{50} represents the drug concentration (mg/kg) required to inhibit the AVP-induced pressor response in pithed rats by 50% on intravenous administration.

methyl-substituted derivative (**8b**) had lower binding affinity for both V_{1A} and V_2 receptors than **2**. In contrast, alkoxy-substituted derivatives (**8c**—**e**) showed potent V_{1A} receptor binding affinity and improvement of selectivity compared with **2**. In particular, the ethoxy-substituted derivative (**8d**) exhibited most potent affinity among alkoxy derivatives and 37-fold selectivity for V_{1A} versus V_2 receptor.

Additionally, chloro derivative (**8f**) and nitro derivative (**8g**) exhibited potent affinity and selectivity for V_{1A} receptor compared with **2**. These results indicated that introduction of an alkoxy group was effective to showing potent affinity and selectivity for the V_{1A} receptor. We reasoned that introduction of two alkoxy groups to the R_1 and R_2 (symmetry position of R_1) positions might produce more potent and selective compounds by synergistic effect, and therefore prepared 2,6-dimethoxy derivative (**8h**). Results showed that compound **8h** exhibited 60-fold selectivity for V_{1A} *versus* V_2 receptor, but that it had lower binding affinity for V_{1A} receptors than the alkoxy derivatives (**8c**—**e**). Consequently, to obtain a compound with favorable V_{1A} receptor binding affinity and selectivity, introduction of one alkoxy (especially ethoxy) group at R_1 position would be effective.

For the next modification, we investigated the influence of various amine substituent groups at the R_3 position of 2-ethoxybenzanilide derivatives, as shown in Table 4. The carbamoyl-substituted derivative (**8i**) had lower binding affinity for V_{1A} and V_2 receptors than **8d**. The alkyl amine substituted derivatives (**8j**—**p**) showed potent V_{1A} receptor binding affinity, but their selectivity was not sufficient. In the investigation of 4′-[(4,4-difluoro-5-methylidene-2,3,4,5-tetrahydro-1*H*-1-benzoazepin-1-yl)carbonyl]-2-phenylbenzanilide derivatives,[9] we found that introduction of a morpholino group showed high V_{1A} receptor selectivity. We, therefore, attempted to introduce a morpholino group at the R_3 position. The morpholino-substituted derivative (**8q**) exhibited most potent V_{1A} receptor binding affinity and 41-fold selectivity in V_{1A} *versus* V_2 receptor. However, the thiomorpholino-substituted derivative (**8r**) showed lower binding affinity and selectivity than **8q**. These results suggested that introduction of moieties including an oxygen or nitrogen atom at both the R_1 and R_3 positions was important to the manifestation of potent and selective V_{1A} receptor antagonist activity.

Subsequently, the compounds (**8d**, **8q**) that showed potent binding affinity and selectivity for the V_{1A} receptor were tested for their binding affinities for cloned human V_{1A} (hV_{1A}) and V_2 (hV_2) receptors (Table 5). Both compounds showed the same potent binding affinity and selectivity for the V_{1A} receptor as in the rat, and no species difference in binding affinity was observed.

Antagonist Activity V_{1A} receptor antagonist activity was determined by measuring inhibition of the AVP-induced diastolic blood pressure (DBP) response in pithed rats after intravenous (i.v.) administration. The dose of compound causing a 50% inhibition of pressor response to AVP (ID_{50}) was calculated. The experimental method used to determine AVP antagonist activity is described in Experimental. Compounds **8d** and **8q** were tested (Table 5). Both compounds significantly suppressed the AVP-induced blood pressure increase. The V_{1A} antagonist activity of these compounds was more effective than that of YM087. In particular, the 4-(*N*,*N*-dimethylamino) piperidine derivative (**8d**) showed 1.4-fold more potent V_{1A} antagonist activity than YM087.

Conclusion

As part of efforts to discover new selective V_{1A} receptor antagonists, we synthesized several 4′-(4,4-difluoro-5-methylidene-2,3,4,5-tetrahydro-1*H*-1-benzoazepin-1-yl)carbonyl derivatives, and evaluated their pharmacological properties. Results showed that introduction of an alkoxy (especially ethoxy) group at the 2′-position of benzanilide was effective to obtaining high potency and selectivity for the V_{1A} receptor. Furthermore, introduction of 4,4-dimethylpiperidino (**8d**) and morpholino (**8q**) groups at the 1-position of carbonylmethylene exhibited more potent affinity and selectivity for V_{1A} receptors.

These compounds possessed powerful antagonist activity for the V_{1A} receptor and are expected to prove valuable as therapeutic tools in the investigation of abnormal secretion of AVP.

Experimental

^{1}H-NMR spectra were obtained on a JEOL JNM-EX90 or JNM-A500 spectrometer and the chemical shifts are expressed in δ (ppm) values with tetramethylsilane as an internal standard. Abbreviations of ^{1}H-NMR signal patterns are as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. Mass spectra were obtained on a JEOL JMS-DX300 spectrometer. Elemental analysis was performed with a Yanaco MT-5. Melting points were determined on a Yanaco MP-500D micro melting point apparatus without correction. Column chromatography on silica gel was performed with Merck KGaA Silica gel 60 (0.040—0.063 mm).

General Procedure for Synthesis of Methyl Ester Derivatives (6a—h) To an ice-cooled mixture of benzoic acid (2.00 mmol) and catalytic *N*,*N*-dimethylformamide (DMF) in CH_2Cl_2 (10 ml) was added oxalyl chloride (3.32 mmol). The mixture was stirred at room temperature for 3 h, diluted with benzene and concentrated *in vacuo* to give a crude acid chloride. To an ice-cooled mixture of **5** (620 mg, 1.67 mmol) and pyridine (5 ml) in CH_2Cl_2 (10 ml) was added a solution of the above acid chloride in CH_2Cl_2 (10 ml). The mixture was stirred at room temperature for 1 h, and then concentrated *in vacuo*. The residue was diluted with ethyl acetate (AcOEt). The organic

layer was washed with a saturated aqueous solution of Na_2CO_3, 1 M HCl and brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was chromatographed on silica gel and eluted with *n*-hexane–AcOEt to give a colorless amorphous substance. All physical and spectral data of methyl ester derivatives are shown in Table 1.

General Procedure for Synthesis of Acetic Acid Derivatives (7a—h) To an ice-cooled solution of **6** (1.55 mmol) in methanol (MeOH) (10 ml) was added lithium hydroxide monohydrate (4.65 mmol) in water (2 ml). The mixture was stirred at room temperature for 7 h, and then concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ and 1 M HCl and extracted with $CHCl_3$. The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The product was purified by recrystallization. All physical and spectral data of acetic acid derivatives are shown in Table 2.

(*Z*)-4′-({4,4-Difluoro-5-[(4,4-dimethylaminopiperidino)carbonylmethylene]-2,3,4,5-tetrahydro-1*H*-1-benzoazepin-1-yl}carbonyl)-2-phenylbenzanilide monohydrochloride (2) To an ice-cooled mixture of **7a** (0.364 mmol) and 1-hydroxybenzotriazole hydrate (HOBt) (0.437 mmol) in CH_2Cl_2 (10 ml) and acetonitrile (CH_3CN) (10 ml) was added 1-ethyl-3-(dimethylaminopropyl) carbodiimide hydrochloride (WSC.HCl) (0.437 mmol) in CH_2Cl_2 (10 ml), and the mixture was stirred at room temperature for 1 h. After being cooled at 0 °C, 4-*N*,*N*-dimethylamino piperidine (0.437 mmol) was added, and the mixture was stirred at room temperature overnight. To the mixture was added 1 M NaOH followed by extraction with $CHCl_3$. The organic layer was dried over anhydrous K_2CO_3 and concentrated *in vacuo*. The residue was chromatographed on a silica gel column using $CHCl_3$–MeOH (95 : 5) as eluent to yield a free amine. The resulting amine was diluted with MeOH, and the solution was cooled at 0 °C. To the solution, 4 N-HCl/AcOEt was added and the mixture was concentrated *in vacuo*, and recrystallized from $CHCl_3$–Et_2O to give 160 mg (0.233 mmol, 72%) of **2** as a colorless powder. mp 240 °C (dec.). ^{1}H-NMR ($CDCl_3$) δ: 1.39—1.80 (2H, m), 2.07 (2H, m), 2.41 (2H, m), 2.66 (1H, m), 2.72 (6H, s), 2.95—3.20 (2H, m), 3.43 (1H, m), 4.04 (1H, m), 4.52 (1H, m), 4.86 (1H, m), 6.78 (1H, s), 6.81 (1H, m), 7.01 (2H, m), 7.19 (1H, m), 7.26—7.43 (8H, m), 7.44—7.60 (5H, m), 10.35 (1H, s). EI-MS *m/z*: 649 (M^++1). *Anal.* Calcd for $C_{39}H_{38}N_4O_3F_2\cdot$HCl: C, 68.36; H, 5.74; N, 8.18; Cl, 5.17; F, 5.55. Found: C, 68.44; H, 5.87; N, 8.09; Cl, 5.07; F, 5.41.

Compounds **8b**—**h** were synthesized in the same manner.

(*Z*)-4′-({4,4-Difluoro-5-[(4,4-dimethylaminopiperidino)carbonylmethylene]-2,3,4,5-tetrahydro-1*H*-1-benzoazepin-1-yl}carbonyl)-2-methylbenzanilide Monohydrochloride (**8b**): Colorless powder. Yield; 62%. mp 204—206 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.40—1.80 (2H, m), 2.09 (2H, m), 2.42 (2H, m), 2.67 (1H, m), 2.71 (6H, s), 2.98—3.21 (2H, m), 4.06 (1H, d, *J*=13 Hz), 4.53 (1H, d, *J*=13 Hz), 4.89 (1H, m), 6.81 (1H, s), 6.85 (1H, d, *J*=8 Hz), 7.09 (2H, d, *J*=8 Hz), 7.20 (1H, t, *J*=8 Hz), 7.25—7.44 (5H, m), 7.52 (1H, d, *J*=8 Hz), 7.58 (2H, d, *J*=8 Hz), 10.39 (1H, s), 10.72 (1H, m). EI-MS *m/z*: 586 (M^+). *Anal.* Calcd for $C_{34}H_{36}N_4O_3F_2\cdot$HCl$\cdot 2H_2O$: C, 61.95; H, 6.27; N, 8.50; Cl, 5.38; F, 5.76. Found: C, 61.99; H, 6.34; N, 8.21; Cl, 5.40; F, 5.68.

(*Z*)-4′-({4,4-Difluoro-5-[(4,4-dimethylaminopiperidino)carbonylmethylene]-2,3,4,5-tetrahydro-1*H*-1-benzoazepin-1-yl}carbonyl)-2-methoxybenzanilide Monohydrochloride (**8c**): Colorless amorphous. Yield; 69%. ^{1}H-NMR (DMSO-d_6) δ: 1.42—1.78 (2H, m), 2.08 (2H, m), 2.42 (2H, m), 2.67 (1H, m), 2.72 (6H, s), 2.99—3.22 (2H, m), 3.43 (1H, m), 3.85 (3H, s), 4.04 (1H, m), 4.52 (1H, m), 4.83 (1H, m), 6.79 (1H, s), 6.83 (1H, m), 7.02—7.21 (5H, m), 7.31 (1H, t, *J*=8 Hz), 7.44—7.62 (5H, m), 10.19 (1H, s), 10.56 (1H, m). FAB-MS *m/z*: 603 (M^++1).

(*Z*)-4′-({4,4-Difluoro-5-[(4,4-dimethylaminopiperidino)carbonylmethylene]-2,3,4,5-tetrahydro-1*H*-1-benzoazepin-1-yl}carbonyl)-2-ethoxybenzanilide Monohydrochloride (**8d**): Colorless amorphous. Yield; 51%. ^{1}H-NMR (DMSO-d_6) δ: 1.35 (3H, s), 1.40—1.80 (2H, m), 2.09 (2H, m), 2.47 (2H, m), 2.68 (1H, m), 2.70 (3H, s), 2.71 (3H, s), 2.95—3.54 (3H, m), 4.06 (1H, m), 4.15 (2H, q, *J*=7 Hz), 4.53 (1H, m), 4.86 (1H, m), 6.81 (1H, s), 6.84 (1H, m), 7.02—7.21 (4H, m), 7.31 (1H, t, *J*=8 Hz), 7.44—7.62 (4H, m), 10.20 (1H, s), 10.76 (1H, m). FAB-MS *m/z*: 617 (M^++1).

(*Z*)-4′-({4,4-Difluoro-5-[(4,4-dimethylaminopiperidino)carbonylmethylene]-2,3,4,5-tetrahydro-1*H*-1-benzoazepin-1-yl}carbonyl)-2-isopropoxybenzanilide Monohydrochloride (**8e**): Colorless amorphous. Yield; 62%. ^{1}H-NMR (DMSO-d_6) δ: 1.31 (6H, d, *J*=6 Hz), 1.40—1.80 (2H, m), 2.08 (2H, m), 2.42 (2H, m), 2.67 (1H, m), 2.72 (6H, s), 2.99—3.22 (2H, m), 3.43 (1H, m), 3.85 (3H, s), 4.04 (1H, m), 4.53 (1H, m), 4.73 (1H, m), 4.86 (1H, m), 6.81 (1H, s), 6.84 (1H, m), 6.98—7.36 (5H, m), 7.31 (1H, m), 7.42—7.70 (5H, m), 10.19 (1H, s), 10.77 (1H, m). FAB-MS *m/z*: 631 (M^++1).

(*Z*)-4′-({4,4-Difluoro-5-[(4,4-dimethylaminopiperidino)carbonylmethylene]-2,3,4,5-tetrahydro-1*H*-1-benzoazepin-1-yl}carbonyl)-2-chlorobenzanilide Monohydrochloride (**8f**): Colorless amorphous. Yield; 17%. ^{1}H-NMR (DMSO-d_6) δ: 1.40—1.80 (2H, m), 2.09 (2H, m), 2.43 (2H, m), 2.67 (1H, m), 2.71 (6H, s), 2.95—3.22 (2H, m), 3.43 (1H, m), 4.06 (1H, m), 4.53 (1H, m), 4.87 (1H, m), 6.82 (1H, s), 6.85 (1H, m), 7.10 (2H, m), 7.20 (1H, t, *J*=8 Hz), 7.31 (1H, t, *J*=7 Hz), 7.41—7.63 (7H, m), 10.61 (1H, m). FAB-MS *m/z*: 607, 609 (M^++1).

(*Z*)-4′-({4,4-Difluoro-5-[(4,4-dimethylaminopiperidino)carbonylmethylene]-2,3,4,5-tetrahydro-1*H*-1-benzoazepin-1-yl}carbonyl)-2-nitrobenzanilide Monohydrochloride (**8g**): Colorless amorphous. Yield; 42%. ^{1}H-NMR (DMSO-d_6) δ: 1.40—1.80 (2H, m), 2.10 (2H, m), 2.43 (2H, m), 2.67 (1H, m), 2.70 (3H, s), 2.71 (3H, s), 3.02—3.24 (2H, m), 3.40 (1H, m), 4.05 (2H, m), 4.53 (1H, m), 4.88 (1H, m), 6.83 (1H, s), 6.86 (1H, m), 7.11 (2H, m), 7.22 (1H, m), 7.32 (1H, t, *J*=6 Hz), 7.52 (2H, m) 7.74—7.78 (2H, m), 7.86 (1H, t, *J*=7 Hz), 8.14 (1H, d, *J*=6 Hz), 10.76 (1H, m), 10.80 (1H, s). FAB-MS *m/z*: 618 (M^++1).

(*Z*)-4′-({4,4-Difluoro-5-[(4,4-dimethylaminopiperidino)carbonylmethylene]-2,3,4,5-tetrahydro-1*H*-1-benzoazepin-1-yl}carbonyl)-2,6-dimethoxybenzanilide Monohydrochloride (**8h**): Colorless amorphous. Yield; 57%. ^{1}H-NMR (DMSO-d_6) δ: 1.40—1.80 (2H, m), 2.10 (2H, m), 2.42 (2H, m), 2.68 (1H, m), 2.70 (3H, s), 2.71 (3H, s), 2.95—3.23 (2H, m), 3.45 (1H, m), 3.73 (6H, s), 4.05 (1H, m), 4.53 (1H, m), 4.87 (1H, m), 6.71 (2H, d, *J*=8 Hz), 6.80 (1H, s), 6.84 (1H, m), 7.06 (1H, m), 7.21 (1H, m), 7.36—7.38 (2H, m), 7.53 (3H, m), 10.31 (1H, s), 10.83 (1H, m). FAB-MS *m/z*: 633 (M^++1).

(*Z*)-4′-[(5-Carbamoylmethylene-4,4-difluoro-2,3,4,5-tetrahydro-1*H*-1-benzoazepin-1-yl)-carbonyl]-2-ethoxybenzanilide (**8i**) To an ice-cooled mixture of **7d** (1.00 mmol) and HOBt (1.10 mmol) in CH_2Cl_2 (10 ml) and CH_3CN (10 ml) was added WSC.HCl (211 mg, 1.10 mmol) in CH_2Cl_2 (10 ml), and the mixture was stirred at room temperature for 1 h. After being cooled at 0 °C, 28% NH_4OH (0.3 ml) was added, and the mixture was stirred at room temperature overnight. To the mixture was added 1 M NaOH and extracted with $CHCl_3$. The organic layer was dried over anhydrous K_2CO_3 and concentrated *in vacuo*. The residue was chromatographed on a silica gel column using $CHCl_3$–MeOH (95 : 5) as eluent, then recrystallized from AcOEt–Et_2O to give 100 mg (0.197 mmol, 20%) of **8i** as a colorless powder. mp 134—139 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.61 (3H, t, *J*=8 Hz), 2.40—2.80 (2H, m), 3.34 (1H, m), 4.23 (2H, d, *J*=8 Hz), 4.86 (1H, d, *J*=8 Hz), 5.66 (1H, s), 6.14 (1H, s), 6.35 (1H, s), 6.72 (1H, d, *J*=8 Hz), 6.94 (1H, d, *J*=8 Hz), 7.00—7.30 (5H, m), 7.38—7.50 (4H, m), 8.24 (1H, d, *J*=8 Hz), 10.16 (1H, s). FAB-MS *m/z*: 506 (M^++1). *Anal.* Calcd for $C_{28}H_{25}N_3O_4F_2\cdot 0.5H_2O$: C, 65.36; H, 5.09; N, 8.17; F, 7.38. Found: C, 65.24; H, 5.13; N, 8.12; F, 7.22.

Compounds **8j**—**r** were synthesized in the same manner.

(*Z*)-4′-{[4,4-Difluoro-5-(*N*-methylcarbamoylmethylene)-2,3,4,5-tetrahydro-1*H*-1-benzoazepin-1-yl]carbonyl}-2-ethoxybenzanilide (**8j**): Colorless powder. Yield; 69%. mp 213—215 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.60 (3H, t, *J*=7 Hz), 2.38 (1H, m), 2.65 (1H, m), 2.96 (3H, d, *J*=5 Hz), 3.31 (1H, s), 4.19 (2H, q, *J*=7 Hz), 4.87 (1H, Br), 6.27 (1H, m), 6.35 (1H, s), 6.69 (1H, d, *J*=8 Hz), 6.91 (1H, d, *J*=8 Hz), 7.00—7.10 (4H, m), 7.23 (1H, t, *J*=7 Hz), 7.40—7.50 (4H, m), 8.22 (1H, d, *J*=6 Hz), 10.15 (1H, s). FAB-MS *m/z*: 520 (M^++1). *Anal.* Calcd for $C_{29}H_{27}N_3O_4F_2$: C, 67.04; H, 5.24; N, 8.09; F, 7.31. Found: C, 66.82; H, 5.33; N, 8.10; F, 7.16.

(*Z*)-2-Ethoxy-4′-{[5-(*N*-ethylcarbamoylmethylene)-4,4-difluoro-2,3,4,5-tetrahydro-1*H*-1-benzoazepin-1-yl]carbonyl}benzanilide (**8k**): Colorless powder. Yield; 77%. mp 197—199 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, t, *J*=7 Hz), 1.60 (3H, t, *J*=7 Hz), 2.40 (1H, m), 2.70 (1H, m), 3.34 (1H, m), 3.44 (1H, m), 4.17 (2H, q, *J*=7 Hz), 4.88 (1H, m), 6.36 (2H, m), 6.67 (1H, d, *J*=8 Hz), 6.68 (1H, d, *J*=8 Hz), 7.00—7.10 (4H, m), 7.23 (1H, t, *J*=7 Hz), 7.40—7.50 (4H, m), 8.22 (1H, d, *J*=6 Hz), 10.14 (1H, s). FAB-MS *m/z*: 534 (M^++1). *Anal.* Calcd for $C_{30}H_{29}N_3O_4F_2\cdot 0.1H_2O$: C, 67.30; H, 5.50; N, 7.85; F, 7.10. Found: C, 67.01; H, 5.64; N, 7.93; F, 6.83.

(*Z*)-4′-({4,4-Difluoro-5-[*N*-(1-propyl)-carbamoylmethylene]-2,3,4,5-tetrahydro-1*H*-1-benzoazepin-1-yl}carbonyl)-2-ethoxybenzanilide (**8l**): Colorless powder. Yield; 79%. mp 214—216 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.98 (3H, t, *J*=7 Hz), 1.60—1.70 (5H, m), 2.40 (1H, m), 2.66 (1H, m), 3.30—3.40 (3H, m), 4.18 (2H, q, *J*=7 Hz), 4.88 (1H, m), 6.36 (2H, br), 6.68 (1H, d, *J*=8 Hz), 6.89 (1H, d, *J*=8 Hz), 7.00—7.10 (4H, m), 7.23 (1H, t, *J*=7 Hz), 7.40—7.50 (4H, m), 8.22 (1H, d, *J*=6 Hz), 10.15 (1H, s). FAB-MS *m/z*: 548 (M^++1). *Anal.* Calcd for $C_{31}H_{31}N_3O_4F_2\cdot 0.2H_2O$: C, 67.55; H, 5.74; N, 7.62; F, 6.89. Found: C, 67.74; H, 6.13; N, 7.65; F, 6.65.

(*Z*)-4′-({4,4-Difluoro-5-[*N*-(2-propyl)carbamoylmethylene]-2,3,4,5-tetrahydro-1*H*-1-benzoazepin-1-yl}carbonyl)-2-ethoxybenzanilide (**8m**): Colorless powder. Yield; 82%. mp>230 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (6H, t, *J*=7 Hz), 1.60 (3H, t, *J*=7 Hz), 2.37 (1H, m), 2.67 (1H, m), 3.33 (1H, m), 4.18 (2H, q, *J*=7 Hz), 4.25 (1H, m), 4.88 (1H, s), 6.11 (1H, m), 6.35 (1H, s),

6.67 (1H, d, J=8 Hz), 6.89 (1H, d, J=8 Hz), 7.00—7.10 (4H, m), 7.23 (1H, t, J=7 Hz), 7.40—7.50 (4H, m), 8.22 (1H, d, J=6 Hz), 10.14 (1H, s). FAB-MS m/z: 548 (M^++1). *Anal.* Calcd for $C_{31}H_{31}N_3O_4F_2 \cdot 0.1H_2O$: C, 67.72; H, 5.73; N, 7.65; F, 6.91. Found: C, 67.56; H, 5.77; N, 7.59; F, 6.71.

(*Z*)-4′-{[5-(*N*-Cyclopropylcarbamoylmethylene)-4,4-difluoro-2,3,4,5-tetrahydro-1*H*-1-benzoazepin-1-yl]carbonyl}-2-ethoxybenzanilide (**8n**): Colorless powder. Yield; 80%. mp>230 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.60—0.70 (2H, m), 0.80—0.90 (2H, m), 1.59 (3H, t, J=7 Hz), 2.38 (1H, s), 2.68 (1H, m), 2.85 (1H, m), 3.28 (1H, m), 4.14 (2H, q, J=7 Hz), 4.87 (1H, s), 6.33 (1H, s), 6.60—6.70 (2H, m), 6.83 (1H, d, J=8 Hz), 7.00—7.10 (4H, m), 7.22 (1H, t, J=7 Hz), 7.30—7.40 (4H, m), 8.20 (1H, d, J=6 Hz), 10.13 (1H, s). FAB-MS m/z: 546 (M^++1). *Anal.* Calcd for $C_{31}H_{29}N_3O_4F_2 \cdot 0.25H_2O$: C, 67.69; H, 5.41; N, 7.64; F, 6.91. Found: C, 67.42; H, 5.42; N, 7.96; F, 6.77.

(*Z*)-4′-{[4,4-Difluoro-5-(*N*,*N*-dimethylcarbamoylmethylene)-2,3,4,5-tetrahydro-1*H*-1-benzoazepin-1-yl]carbonyl}-2-ethoxybenzanilide (**8o**): Colorless powder. Yield; 84%. mp 195—198 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.61 (3H, t, J=7 Hz), 2.30—2.80 (2H, m), 3.04 (3H, s), 3.09 (3H, s), 3.28 (1H, m), 4.26 (2H, q, J=7 Hz), 5.04 (1H, m), 6.34 (1H, s), 6.72 (1H, d, J=8 Hz), 6.99 (1H, d, J=8 Hz), 7.10—7.50 (9H, m), 8.25 (1H, d, J=6 Hz), 10.18 (1H, s). FAB-MS m/z: 534 (M^++1). *Anal.* Calcd for $C_{30}H_{29}N_3O_4F_2 \cdot 0.5H_2O$: C, 66.41; H, 5.57; N, 7.74; F, 7.00. Found: C, 66.37; H, 5.84; N, 7.73; F, 6.70.

(*Z*)-4′-{[5-(*N*,*N*-Diethylcarbamoylmethylene)-4,4-difluoro-2,3,4,5-tetrahydro-1*H*-1-benzoazepin-1-yl]carbonyl}-2-ethoxybenzanilide (**8p**): Colorless powder. Yield; 73%. mp 164—165 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.21 (6H, t, J=8 Hz), 1.60 (3H, t, J=7 Hz), 2.40—2.80 (2H, m), 3.30 (1H, m), 3.67 (4H, q, J=8 Hz), 4.26 (2H, q, J=7 Hz), 5.05 (1H, m), 6.38 (1H, s), 6.71 (1H, d, J=8 Hz), 6.98 (1H, d, J=8 Hz), 7.00—7.30 (5H, m), 7.36 (1H, t, J=7 Hz), 7.40—7.50 (3H, m), 8.24 (1H, d, J=6 Hz), 10.17 (1H, s). FAB-MS m/z: 562 (M^++1). *Anal.* Calcd for $C_{32}H_{33}N_3O_4F_2 \cdot 0.5H_2O$: C, 67.35; H, 6.01; N, 7.37; F, 6.66. Found: C, 67.56; H, 5.98; N, 7.43; F, 6.63.

(*Z*)-4′-[(4,4-Difluoro-5-morpholinocarbamoylmethylene-2,3,4,5-tetrahydro-1*H*-1-benzoazepin-1-yl)carbonyl]-2-ethoxybenzanilide (**8q**): Colorless powder. Yield; 82%. mp 144—147 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.61 (3H, t, J=7 Hz), 2.40—2.80 (2H, m), 3.30 (1H, m), 3.58 (2H, m), 3.74 (6H, m), 4.26 (2H, q, J=7 Hz), 5.05 (1H, m), 6.33 (1H, s), 6.74 (1H, d, J=8 Hz), 6.99 (1H, d, J=8 Hz), 7.10—7.60 (9H, m), 8.25 (1H, d, J=6 Hz), 10.17 (1H, s). FAB-MS m/z: 576 (M^++1). *Anal.* Calcd for $C_{32}H_{31}N_3O_5F_2$: C, 66.77; H, 5.43; N, 7.30; F, 6.60. Found: C, 66.81; H, 5.35; N, 7.33; F, 6.63.

(*Z*)-4′-[(4,4-Difluoro-5-thiomorpholinocarbamoylmethylene-2,3,4,5-tetrahydro-1*H*-1-benzoazepin-1-yl)carbonyl]-2-ethoxybenzanilide (**8r**): Colorless powder. Yield; 42%. mp 156—158 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.61 (3H, t, J=7 Hz), 2.27—2.86 (6H, m), 3.26 (1H, m), 3.70—4.14 (4H, m), 4.26 (2H, q, J=7 Hz), 5.02 (1H, m), 6.33 (1H, s), 6.74 (1H, m), 6.99 (1H, t, J=8 Hz), 7.07—7.29 (6H, m), 7.36 (1H, m), 7.53 (3H, m), 8.24 (1H, m), 10.17 (1H, s). FAB-MS m/z: 592 (M^++1). *Anal.* Calcd for $C_{32}H_{31}N_3O_4SF_2$: C, 64.96; H, 5.28; N, 7.10; S, 5.42; F, 6.42. Found: C, 63.07; H, 5.26; N, 6.86; S, 5.26; F, 6.25.

Receptor Binding Assay: For the Rat Receptors[12,13] Binding assays were performed using [^{3}H]AVP on plasma membranes prepared from rat liver or kidney. Plasma membrane preparations were incubated with various concentrations of [^{3}H]AVP (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 addition of 3 ml of ice-cooled Tris buffer (50 mM Tris–HCl, pH 7.5, 5 mM $MgCl_2$), followed immediately by filtration using glass filters. The filters were rinsed twice with Tris buffer and radioactivity retained on them was counted with a liquid scintillation counter. Specific binding was calculated as the total binding minus non-specific binding, which was determined using 1 μM unlabeled AVP. The concentration of test compound that caused 50% inhibition (IC_{50}) of the specific binding of [^{3}H]AVP was determined by regression analysis of the displacement curve. Inhibitory dissociation constant (K_i) was calculated from the following formula: $K_i = IC_{50}/(1+[L]/K_d)$, where [L] is concentration of radioligand present in the tubes and K_d is the dissociation constant of radioligand obtained from the Scatchard plot.

Receptor Binding Assay: For the Cloned Human Receptors[12,13] The cloned human AVP receptor subtypes were stably expressed in CHO cells and plasma membranes prepared according to the reported protocols.

V_{1A} Receptor Antagonistic Activity[12,13] 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 the stabilization of 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.

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