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-benzazepin-1-yl)carbonyl]benzanilide Derivatives

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A series of compounds structurally related to 4′-[(2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)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 phenyl or a 4-substituted phenyl group into the *ortho* position of the benzoyl moiety resulted in an increase in both binding affinity and antagonistic activity. The 2-(4-methylphenyl) derivative (1g) exhibited high antagonistic activities for both V_{1A} (8.6-fold) and V_2 (38-fold) receptors and high oral activity (8.6-fold) compared with the 2-methyl lead compound (1a).[1] Datail of the synthesis and the pharmacological properties of this series are presented.

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

Arginine vasopressin (AVP) is a peptide hormone which is released from the posterior pituitary and exerts a variety of biological effects. Recently, several nonpeptide V_{1A}-selective and V_2-selective antagonists have been reported[1–4] and some of them are under clinical testing (Fig. 1).

Many reports have indicated that AVP plays a role in congestive heart failure (CHF), and that patients with CHF show a high level of plasma AVP.[5] Therefore, blockade of both V_{1A} and V_2 receptors might be a beneficial therapeutic strategy in conditions such as CHF. On the basis of this hypothesis, we have been attempting to develop new AVP antagonists for both V_{1A} and V_2 receptors. In the course of searching for leads, 4′-[(2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)carbonyl]benzanilide derivatives attracted our attention. It was reported by Ogawa *et al.*[1] that introduction of a lipophilic group such as methyl or chloro into the *ortho* or *meta* position on the benzoyl moiety of these compounds enhanced the AVP receptor affinities and that the 2-methyl derivative (**1a**, Fig. 2) had similar affinities for both V_{1A} and V_2 receptors.

Therefore, modification studies of the lead compound **1a** were focused on the introduction of an aromatic ring as a more lipophilic group in place of a methyl group on the benzoyl moiety. In this report, the phenyl-substituted compounds shown in Fig. 2 were investigated. Herein, the synthesis and the biological activity of these compounds are described.

Chemistry

Phenyl-substituted 4′-[(2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)carbonyl]benzanilide derivatives (**1b—p**) were synthesized according to the routes shown in Chart 1.

Among the intermediate phenyl-substituted benzoic acids, the commercially unavailable 3-phenyl (**6c**) and 2-(substituted phenyl) derivatives (**6e—i** and **6o**) were prepared by modification of the general procedure[6] shown in Chart 1. Lithiation of the bromobenzene derivatives (**2**) with butyllithium followed by transmetalation with zinc chloride gave the intermediates (**3**). Coupling of the iodobenzoic acid esters (**4**) with **3** in the presence of a nickel catalyst gave phenyl-substituted benzoic acid esters (**5**), which were then hydrolyzed to give carboxylic acids (**6**). The 2-[(4-dimethylamino)phenyl]benzoic acid (**6n**) was obtained from 2-(4-nitrophenyl)benzoic acid (**6k**)[7] by reductive alkylation *via* the amino derivative.

The desired benzanilide derivatives (**1**) were prepared by condensation of **6** and 1-(4-aminobenzoyl)-2,3,4,5-tetrahydro-1*H*-1-benazepine (**8**)[1] by the acid chloride method. The 2-(4-aminophenyl) derivative (**1l**) was obtained from the 2-(4-nitrophenyl) derivative (**1k**) by catalytic hydrogenation, and acetylation of **1l** gave the (4-acetamidophenyl) derivative (**1m**). The 2-(4-hydroxyphenyl) derivative (**1p**) was obtained from the 2-(4-methoxyphenyl) derivative (**1o**) by demethylation with boron tribromide.

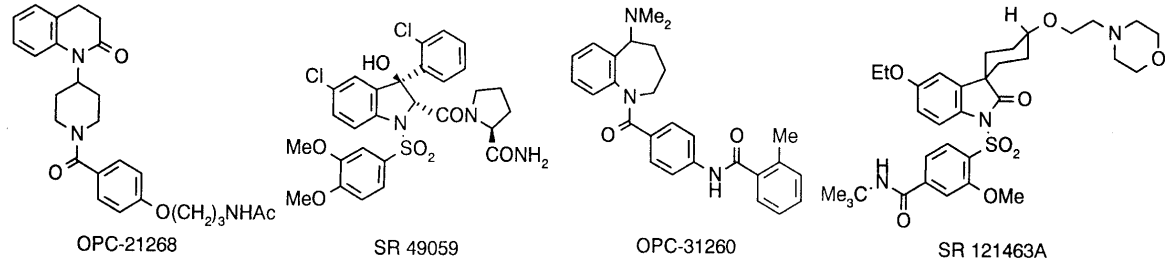

Fig. 1

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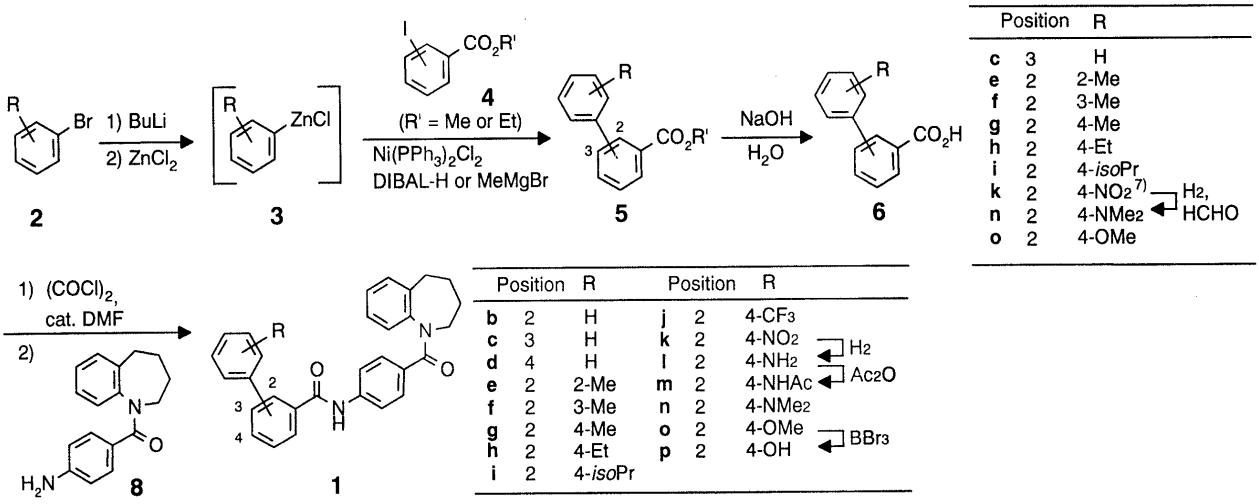
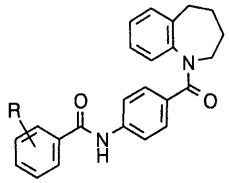


Chart 1

Table 1. Receptor-Binding Affinities for Phenyl-Substituted Benzanilide Derivatives



No.	R	Yield (%)[a]	mp (°C) (lit.)	Formula[b]	^{1}H-NMR (DMSO-d_6) δ	Binding affinity (pK_i)		
						V_{1A}[c]	V_2[d]	OT[e]
OPC-31260						6.71	8.01	6.18
1a	2-Me		224—225 (225.5—226.5[f])			8.09	8.14	7.52
1b	2-Ph	41	215—216	$C_{30}H_{26}N_2O_2 \cdot 1/2H_2O$	1.4—2.2 (4H, m), 2.6—3.1 (3H, m), 4.9—5.1 (1H, m), 6.6—8.1 (17H, m)[i]	7.85	8.12	7.20
1c	3-Ph	49	NT[g]	$C_{30}H_{26}N_2O_2 \cdot 1/5H_2O$[h]	1.4—2.2 (4H, m), 2.7—3.1 (3H, m), 4.9—5.1 (1H, m), 6.5—8.0 (17H, m)[i]	5.78	5.47	<5
1d	4-Ph	74	>250	$C_{30}H_{26}N_2O_2 \cdot 1/2H_2O$	1.4—2.1 (4H, m), 2.7—3.1 (3H, m), 4.9—5.1 (1H, m), 6.6—8.1 (17H, m)[i]	5.94	5.07	<5
1e	2-(2-Me)Ph	34	192—193	$C_{31}H_{28}N_2O_2 \cdot 1/3H_2O$	1.1—2.2 (7H, m), 2.6—3.1 (3H, m), 4.6—5.1 (1H, m), 6,6—7.7 (16H, m)	8.57	8.96	8.58
1f	2-(3-Me)Ph	41	195—196	$C_{31}H_{28}N_2O_2 \cdot 1/3H_2O$	1.1—2.1 (4H, m), 2.22 (3H, s), 2.6—3.1 (3H, m), 4.6—5.1 (1H, m), 6.6—7.7 (16H, m)	7.81	8.94	6.62
1g	2-(4-Me)Ph	66	180—181	$C_{31}H_{28}N_2O_2$	1.1—2.1 (4H, m), 2.27 (3H, s), 2.6—3.1 (3H, m), 4.6—5.1 (1H, m), 6.6—7.7 (16H, m)	8.07	8.61	7.47
1h	2-(4-Et)Ph	32	178—179	$C_{32}H_{30}N_2O_2 \cdot 1/2Et_2O$	1.0—2.3 (7H, m), 2.5—3.1 (5H, m), 4.6—5.1 (1H, m), 6.6—7.7 (16H, m)	7.69	8.75	<5
1i	2-(4-isoPr)Ph	26	202—203	$C_{33}H_{32}N_2O_2 \cdot 1/3H_2O$	1.0—2.3 (10H, m), 2.6—3.1 (4H, m), 4.6—5.1 (1H, m), 6.6—7.7 (16H, m)	6.89	7.67	<5
1j	2-(4-CF_3)Ph	84	136—138	$C_{31}H_{25}F_3N_2O_2 \cdot 1/5CHCl_3$	1.1—2.1 (4H, m), 2.6—3.1 (3H, m), 4.6—5.0 (1H, m), 6.6—7.9 (16H, m)	6.10	6.68	<5
1k	2-(4-NO_2)Ph	57	247—249	$C_{30}H_{25}N_3O_4 \cdot 3/4H_2O$	1.1—2.2 (4H, m), 2.6—3.1 (3H, m), 4.6—5.0 (1H, m), 6.6—8.4 (16H, m)	7.01	7.02	6.32
1l	2-(4-NH_2)Ph	80	249—250	$C_{30}H_{27}N_3O_2 \cdot 1/3H_2O$	1.0—2.2 (4H, m), 2.6—3.1 (3H, m), 4.5—5.1 (1H, m), 5.09 (2H, s), 6.4—7.6 (16H, m)	8.56	10.4	6.86
1m	2-(4-NHAc)Ph	41	>250	$C_{32}H_{29}N_3O_3 \cdot 1/3H_2O$	1.1—2.1 (4H, m), 2.03 (3H, s), 2.6—3.1 (3H, m), 4.6—5.1 (1H, m), 6.6—7.7 (16H, m)	7.56	6.98	5.86
1n	2-(4-NMe_2)Ph	38	215—217	$C_{32}H_{31}N_3O_2 \cdot 1/3H_2O$	1.1—2.2 (4H, m), 2.6—3.1 (3H, m), 2.88 (6H, s), 4.6—5.0 (1H, m), 6.6—7.6 (16H, m)	8.24	8.59	6.38
1o	2-(4-OMe)Ph	61	196—197	$C_{31}H_{28}N_2O_3 \cdot 1/2Me_2CO$	1.1—2.2 (4H, m), 2.6—3.1 (3H, m), 3.73 (3H, s), 4.6—5.1 (1H, m), 6.6—7.7 (16H, m)	8.19	7.84	6.31
1p	2-(4-OH)Ph	86	211—212	$C_{30}H_{26}N_2O_3 \cdot 1/3H_2O$	1.1—2.2 (4H, m), 2.6—3.1 (3H, m), 4.6—5.1 (1H, m), 6.6—7.7 (16H, m), 9.42 (1H, s)	7.56	9.47	7.08

a) Yields were based on the final step of the indicated synthetic method and were not optimized. *b*) Analytical result 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. 1. *g*) NT: not tested (amorphous solid). *h*) H (calcd 5.91, Found 6.39). *i*) Solvent was $CDCl_3$.

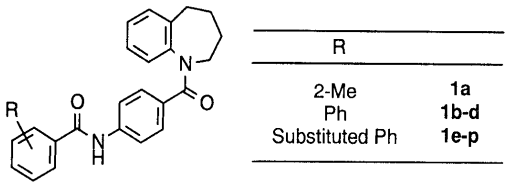


Fig. 2

Results and Discussion

Binding Affinity Results of the *in vitro* AVP and oxytocin (OT) receptor-binding assay are shown in Table 1. Initially, the phenyl-substituted derivatives (**1b—d**) were prepared to examine the effects of the substituent position. Among these compounds, the 2-phenyl derivative (**1b**) showed affinities similar to those of the 2-methyl derivative (**1a**) for both V_{1A} and V_2 receptors. On the other hand, the 3- and 4-phenyl derivatives (**1c** and **1d**) showed poor affinities for both V_{1A} and V_2 receptors.

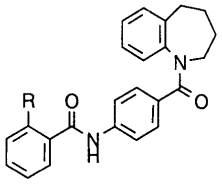
Therefore, the effect of the introduction of various substituent groups on the 2-phenyl moiety of **1b** was investigated. To examine the effects of the substituent position, the methyl-substituted derivatives (**1e—g**) were prepared. All the compounds showed high affinity, but the 2-methyl derivative (**1e**) showed high affinities for not only AVP receptors, but also the OT receptor, and the 3-methyl derivative (**1f**) exhibited 13-fold selectivity for V_2 *versus* V_{1A} receptors. In contrast, the 4-methyl derivative (**1g**) showed potent affinities for both V_{1A} and V_2 receptors and less affinity for the OT receptor. We concluded that the *para* substituent position was the most favorable for our purposes.

On the basis of these studies, a number of *para*-substituted derivatives of **1b** were synthesized. The results for the ethyl (**1h**) and the isopropyl (**1i**) groups indicated a trend of decreasing affinity with increasing bulk. Introduction of an electron-withdrawing trifluoromethyl group (**1j**) resulted in nearly 100-fold less affinity as compared with **1g** for both V_{1A} and V_2 receptors, although the trifluoromethyl group is similar in size to methyl. Likewise, a nitro group (**1k**) caused over a 10-fold decrease in affinity compared with **1g**.

On the other hand, introduction of an electron-donating group such as amino (**1l**), acetamido (**1m**), dimethylamino (**1n**), methoxyl (**1o**) or hydroxyl (**1p**) caused little change in V_{1A} receptor affinity compared with **1g**. However, **1l** and **1p** showed 62- and 7.2-fold increases in V_2 receptor affinity compared with **1g**, respectively. As a result, **1l** and **1p** showed high selectivity for V_2 *versus* V_{1A} receptor (70-fold (**1l**) and 80-fold (**1p**)).

Antagonistic Activity AVP-antagonistic activities were determined by measuring the inhibition of the AVP-induced diastolic blood pressure response (for V_{1A} receptor) and the effect on urine volume (for V_2 receptor) after intravenous (i.v.) administration. The oral activity was determined by measuring the effect on urine volume. Compounds **1b**, **1g**, and **1n**, which exhibited potent binding affinities for both V_{1A} and V_2 receptors, were selected and tested (Table 2). All the compounds, especially **1g**, exhibited high activities for both V_{1A} (8.6-fold) and V_2 (38-fold) receptors compared with the lead compound **1a**.

Table 2. AVP-Antagonistic Activities for Phenyl-Substituted Benzanilide Derivatives



No.	R	V_{1A}	V_2	
		ID_{50} (mg/kg)[a]	ED_3 (mg/kg)[b]	UV (ml)[c]
OPC-31260		5.71	2.07	6.65±0.41
1a	Me	0.3	10.3	0.38±0.16
1b	Ph	0.011	1.09	0.67±0.18
1g	(4-Me)Ph	0.035	0.27	3.26±0.59
1n	(4-NMe_2)Ph	0.15	1.71	0.17±0.11

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.

Furthermore, **1g** showed an 8.6-fold increase in oral activity compared with **1a**. Thus, the antagonistic activity and oral activity were enhanced by suitable modification of the substituent group on the benzoyl moiety of 4′-[(2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)carbonyl]-benzanilide.

Conclusion

Phenyl-substituted 4′-[(2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)carbonyl]benzanilide derivatives were synthesized to develop AVP antagonists for both V_{1A} and V_2 receptors, and their pharmacological properties were evaluated. The introduction of 2-phenyl and 2-(4-substituted phenyl) groups resulted in potent antagonistic activities towards both V_{1A} and V_2 receptors, as exemplified by **1b**, **1g**, and **1n**. In these series, the 2-(4-methylphenyl)-substituted derivative (**1g**) was a highly effective antagonist *in vitro* and *in vivo*, with good oral availability. Dual V_{1A} and V_2 receptor antagonists such as **1g** may be useful as pharmacological tools to elucidate the pathological role of AVP.

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

Ethyl 3-Phenylbenzoate (5c) A solution of butyllithium in hexane (1.7 M, 6.7 ml) was added to a solution of bromobenzene (1.57 g) in tetrahydrofuran (THF) (20 ml) at −78 °C, and the mixture was stirred for 30 min. It was gradually warmed to −20 °C, stirred for 15 min, and then cooled to −78 °C. To this mixture was added a solution of $ZnCl_2$ in THF (1.4 M, 7.8 ml), and the whole was stirred for 30 min at −78 °C. In another flask an activated nickel catalyst solution was prepared as follows. A solution of diisobutylaluminum hydride (DIBAL-H) in hexane (1.0 M, 1.0 ml) was added to a solution of $Ni(PPh_3)_2Cl_2$ (0.65 g) in diethylether (Et_2O) (10 ml) at 0 °C and the mixture was stirred for 15 min.

Then a solution of ethyl 3-iodobenzoate (1.5 ml) in Et_2O (10 ml) was added dropwise at 0 °C and the whole was stirred for 15 min. The catalyst solution was cooled to −78 °C, and the solution of zinc reagent was added dropwise to it, then the mixture was stirred for 18 h at room temperature. It was cooled to 0 °C, and Celite (5 g) and water (10 ml) were added. The insoluble materials were removed by filtration, and the filtrate was concentrated. The residue was dissolved in $CHCl_3$, and the solution was washed with brine, dried, and concentrated. The residue was chromatographed over silica gel using 40 : 1 hexane–ethyl acetate (AcOEt) to give **5c** (0.99 g, 44%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.42 (3H, t), 4.40 (2H, q), 7.3—7.7 (7H, m), 8.03 (1H, d), 8.28 (1H, s). MS *m/z*: 226 (M^+).

3-Phenylbenzoic Acid (6c) A mixture of a solution of **5c** (0.99 g) in ethanol (9 ml) and 1 N NaOH (4.5 ml) was stirred for 18 h at room temperature, then concentrated. The residue was dissolved in water. This solution was treated with 1 N HCl (8 ml) and the mixture was extracted with AcOEt. The organic layer was washed with brine, dried, and concentrated. The resulting solid was collected by filtration to give **6c** (690 mg, 79.5%) as a colorless powder, mp 163—165 °C (lit.[8] 163—165 °C). ^{1}H-NMR ($CDCl_3$) δ: 7.3—7.6 (6H, m), 7.86 (1H, d), 8.10 (1H, d), 8.37 (1H, s). MS *m/z*: 198 (M^+).

2-(2-Methylphenyl)benzoic Acid (6e) In the same manner as described for **5c**, crude methyl 2-(2-methylphenyl)benzoate (**5e**) was prepared from methyl 2-iodobenzoate (4.6 g) and 2-bromotoluene (3.0 g) using MeMgBr in THF (1.0 M, 1.83 ml) in place of DIBAL-H. **5e** was hydrolyzed without purification to gave **6e** (3.6 g, 96%) as a colorless powder, mp 101—104 °C (lit.[9] 104—105 °C). ^{1}H-NMR ($CDCl_3$) δ: 2.07 (3H, s), 7.0—8.2 (8H, m). MS *m/z*: 212 (M^+).

In the same manner, **6f**—**i** and **6o** were synthesized.

2-(3-Methylphenyl)benzoic Acid (6f) Pale yellow powder (99%), mp 95—97 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.38 (3H, s), 7.0—8.2 (8H, m). MS *m/z*: 212 (M^+).

2-(4-Methylphenyl)benzoic Acid (6g) Pale yellow powder (47%), mp 148—150 °C (lit.[10] 148—150 °C). ^{1}H-NMR ($CDCl_3$) δ: 2.39 (3H, s), 7.2—8.0 (8H, m). MS *m/z*: 212 (M^+).

2-(4-Ethylphenyl)benzoic Acid (6h) Pale yellow powder (92%), mp 127—130 °C (lit.[11] 129—131 °C). ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, t), 2.70 (2H, q), 7.2—8.0 (8H, m). MS *m/z*: 226 (M^+).

2-(4-Isopropylphenyl)benzoic Acid (6i) Pale yellow powder (89%), mp 103—106 °C (lit.[11] 106.5—107.5 °C). ^{1}H-NMR ($CDCl_3$) δ: 1.29 (6H, d), 2.95 (1H, m), 7.2—8.0 (8H, m). MS *m/z*: 240 (M^+).

2-(4-Methoxyphenyl)benzoic Acid (6o) Colorless powder (29%), mp 146—149 °C (lit.[12] 146—148 °C). ^{1}H-NMR ($CDCl_3$) δ: 3.79 (3H, s), 6.9—7.8 (8H, m). MS *m/z*: 228 (M^+).

2-[4-(Dimethylamino)phenyl]benzoic Acid (6n) A mixture of 2-(4-nitrophenyl)benzoic acid (**6k**)[7] (500 mg) and 10% Pd–C (100 mg) in acetic acid (10 ml) and *N*,*N*-dimethylformamide (DMF) (10 ml) was stirred for 18 h under a hydrogen atmosphere (1 atm) at room temperature. Then 35% formalin (0.9 ml) was added and the mixture was stirred for 2 h under a hydrogen atmosphere (1 atm) at room temperature. The catalyst was removed by filtration and the filtrate was concentrated to give **6n** (quantitative yield) as a colorless oil. ^{1}H-NMR (DMSO-d_6) δ: 2.90 (6H, s), 6.74 (1H, d), 7.1—7.7 (7H, m). MS *m/z*: 241 (M^+).

3-Phenyl-4′-[(2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)carbonyl]benzanilide (1c) To an ice-cooled solution of **6c** (220 mg) in CH_2Cl_2 (10 ml) were added a catalytic amount of DMF and $(COCl)_2$ (190 mg), and the mixture was stirred for 1 h. It was concentrated and the residue was dissolved in CH_2Cl_2 (5 ml). This solution was added dropwise to an ice-cooled solution of 1-(4-aminobenzoyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (**8**)[1] (266 mg) and Et_3N (100 mg) in CH_2Cl_2 (10 ml) and the mixture was stirred for 1 h. It was then washed with brine, dried, and concentrated. The residue was chromatographed over silica gel using $CHCl_3$ and crystallized from Et_2O–hexane to give **1c** (220 mg, 49%) as a colorless amorphous solid. ^{1}H-NMR ($CDCl_3$) δ: 1.4—2.2 (4H, m), 2.7—3.1 (3H, m), 4.9—5.1 (1H, m), 6.5—8.0 (17H, m). FAB-MS *m/z*: 447 ($M^+ + 1$). *Anal.* Calcd for $C_{30}H_{26}N_2O_2 \cdot 1/5H_2O$: C, 80.05; H, 5.91; N, 6.22. Found: C, 80.04; H, 6.39; N, 6.12.

In the same manner, compounds **1a**, **1b**, **1d**—**k**, **1n**, and **1o** were synthesized.

2-(4-Aminophenyl)-4′-[(2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)carbonyl]benzanilide (1l) A mixture of 2-(4-nitrophenyl)-4′-[(2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)carbonyl]benzanilide (**1k**) (3.1 g) and 10% Pd–C (300 mg) in THF (45 ml) and MeOH (45 ml) was stirred for 18 h under a hydrogen atmosphere (1 atm) at room temperature. Raney-nickel (0.75 g) was added and the whole was stirred for 1 h under a hydrogen atmosphere (1 atm) at 45 °C. It was concentrated, and the residue was dissolved in DMF. The catalyst was removed by filtration, and the filtrate was concentrated to give a crude solid (2.32 g). This (250 mg) was purified by washing with hot MeOH to give **1l** (140 mg, 23%) as a colorless powder, mp 249—250 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.0—2.2 (4H, m), 2.6—3.1 (3H, m). 4.5—5.1 (1H, m), 5.09 (2H, s), 6.4—7.6 (16H, m). FAB-MS *m/z*: 462 ($M^+ + 1$). *Anal.* Calcd for $C_{30}H_{27}N_3O_2 \cdot 1/3H_2O$: C, 77.07; H, 5.96; N, 8.99. Found: C, 77.18; H, 6.08; N, 8.95.

2-(4-Acetamidophenyl)-4′-[(2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)carbonyl]benzanilide (1m) A solution of **1l** (250 mg) in pyridine (5 ml) was cooled on ice, then Ac_2O (100 mg) and a catalytic amount of 4-dimethylaminopyridine were added, and the mixture was stirred for 1 h at room temperature. It was poured into water, and the whole was extracted with $CHCl_3$. The organic layer was washed with 1 N NaOH and 1 N HCl, dried, and concentrated. The residue was chromatographed over silica gel using 30 : 1 $CHCl_3$–MeOH and crystallized from $CHCl_3$–Et_2O to give **1m** (113 mg, 42%) as a colorless powder, mp >250 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.1—2.1 (4H, m), 2.03 (3H, s), 2.6—3.1 (3H, m), 4.6—5.1 (1H, m), 6.6—7.7 (16H, m). FAB-MS *m/z*: 504 ($M^+ + 1$). *Anal.* Calcd for $C_{32}H_{29}N_3O_3 \cdot 1/3H_2O$: C, 75.43; H, 5.87; N, 8.25. Found: C, 75.45; H, 5.88; N, 8.17.

2-(4-Hydroxyphenyl)-4′-[(2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)carbonyl]benzanilide (1p) A solution of BBr_3 in CH_2Cl_2 (1 M, 3.27 ml) was added dropwise to a suspension of 2-(4-methoxyphenyl)-4′-[(2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)carbonyl]benzanilide (**1o**) (312 mg) in CH_2Cl_2 (30 ml) under an argon atmosphere at −78 °C. The mixture was gradually warmed to room temperature, stirred for 1 h, and cooled to −78 °C. Then MeOH (1 ml) was added, and the whole was gradually warmed to room temperature and stirred for 30 min. It was concentrated, and the residue was chromatographed over silica gel using 5 : 1 $CHCl_3$–AcOEt. The product was crystallized from $CHCl_3$–Et_2O to give **1p** (260 mg, 85%) as a colorless powder, mp 211—212 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.1—2.2 (4H, m), 2.6—3.1 (3H, m), 4.6—5.1 (1H, m), 6.6—7.7 (16H, m), 9.42 (1H, s). FAB-MS *m/z*: 463 ($M^+ + 1$). *Anal.* Calcd for $C_{30}H_{26}N_2O_3 \cdot 1/3H_2O$: C, 76.91; H, 5.74; N, 5.98. Found: C, 77.02; H, 5.56; N, 5.97.

Receptor Binding Assay[13] 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. 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 Antagonistic Activity[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 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 Antagonistic Activity[13] Rats were deprived of drinking water for 16—20 h to stimulate endogenous AVP secretion. Compounds or vehicle was administered intravenously or orally 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.

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