Articles

Novel Design of Nonpeptide AVP V_2 Receptor Agonists: Structural Requirements for an Agonist Having 1-(4-Aminobenzoyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine as a Template

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The discovery of a series of nonpeptide arginine vasopressin V_2 receptor agonists is described. After identifying the aniline derivative **8** as our lead compound from the metabolites of compound **7** that showed antidiuretic activity by po administration to Brattleboro rats, improvements in the in vitro potency involving evaluations of the structural requirements for agonist action and optimizing the structure of the benzoyl moiety have been intensively undertaken. These studies led to compounds **16g**, **19a**, and **23b**,**h**,**i** that show potent agonist activity for the V_2 receptor.

Introduction

Arginine vasopressin (AVP) is a well-known hormone that exerts its major actions through two well-defined receptor subtypes in the periphery: the V_{1a} and V_2 receptors.[1] The V_{1a} receptor subtype exists mainly in vascular smooth muscle cells, platelets, liver, adrenal, and uterus, and the V_2 receptor is present in the kidney. Vasopressin-induced antidiuresis, mediated by renal epithelial V_2 receptors, helps to maintain normal plasma osmolality, blood volume, and blood pressure. Another subtype of the AVP receptor was found in the pituitary as a V_{1b} receptor that is involved in the corticotropic response to stress through regulation of ACTH secretion and the potentiating effect on the corticotropin-releasing hormone (CRH). Although many attempts to develop a V_2 antagonist for treating diseases characterized by excess renal reabsorption of free water have been reported, because V_2 antagonists may correct the fluid retention and hyponatremia observed in congestive heart failure, liver cirrhosis, and nephrotic syndrome, marked species differences and inconsistencies have been revealed between the in vivo and in vitro assay systems as reported in the case of **1** (Figure 1).[2] This compound showed antagonist activity in an in vitro study and in animal models including the rhesus monkey but showed full antidiuretic response in humans. We assumed that such species differences originated from the structural resemblance of the peptide derivatives to AVP itself; therefore, we initiated attempts to discover some structurally diverse nonpeptides having an affinity for the AVP receptors, to overcome this problem.

After our reports of the nonpeptide V_{1a} antagonist (**2**),[3] some studies[4] pointed out the possibility of species differences with respect to the binding affinity even with a nonpeptide ligand having a structure different from that of AVP using human tissues (K_i rat liver = 32 ± 5.2 nM, human liver = 14 000 nM).[4g] Though the same issue for the peptide ligands was apparently found with the nonpeptide, compound **3** was found to be an orally active nonpeptide V_2 antagonist as the result of our continuous efforts[5] and was able to demonstrate its aquaretic effect in clinical tests.[6]

The definitive characterization of vasopressin receptors and their function has become possible since the successive cloning studies of the V_{1a}, V_2, and V_{1b} receptors.[7] These receptors were confirmed to be a superfamily of the G-protein-coupled receptors (GPCRs).

From our efforts to find more potent V_2 receptor antagonists, **4** (Tolvaptan) inhibited the [^{3}H]AVP binding to human V_2 receptors (K_i = 0.43 ± 0.06 nM) more potently than AVP (K_i = 0.79 ± 0.08 nM) or **3** (K_i = 9.42 ± 0.90 nM). The antagonistic action of **4** was confirmed by the inhibition of cAMP production induced by AVP using the human receptor expressed HeLa cells[8] and also by clinical tests.

Although the V_2 agonist may be beneficial for the treatment of central diabetes insipidus, urinary incontinence, and nocturnal enuresis, no report was found for agonists having a nonpeptide structure that may be beneficial for oral bioavailability. In central diabetes insipidus, excessive diuresis occurs due to lack of

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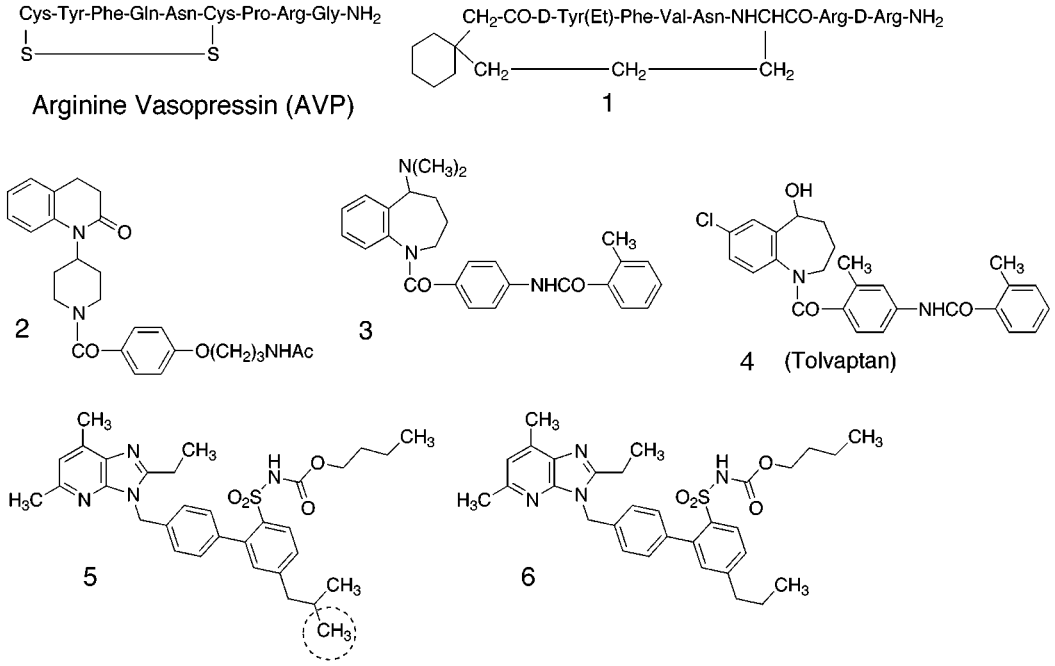


Figure 1. Structures of AVP and compounds **1**−**6**.

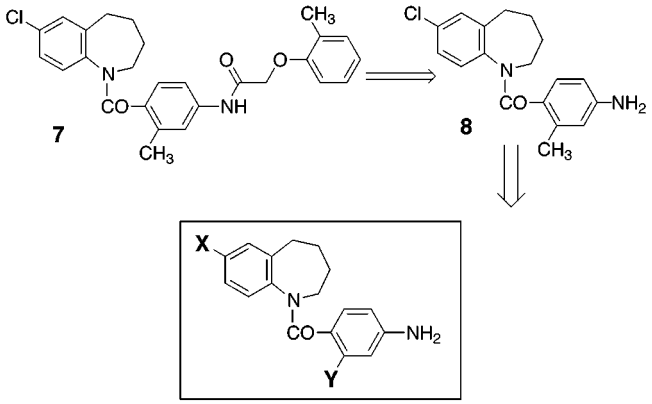


Figure 2. Preliminary design of AVP V_2 receptor agonists.

vasopressin release from the pituitary. 1-Desamino-8-D-arginine vasopressin (DDAVP), a peptide derivative of AVP, and AVP itself are clinically used for the treatment of such diseases. Recently, nonpeptide agonists for the seven transmembraine G-protein-coupled receptors have been reported in the angiotensin system[9a−h] and the cholecystokinin system.[9i,j] We were very interested to learn that two nonpeptide ligands that differ by only a single methyl group but have agonist (compound **5** Figure 1) and antagonist (compound **6**) properties in vivo were characterized on the cloned angiotensin AT1 receptor. This may be the first report that the additional functional group contributes to producing the agonist action.

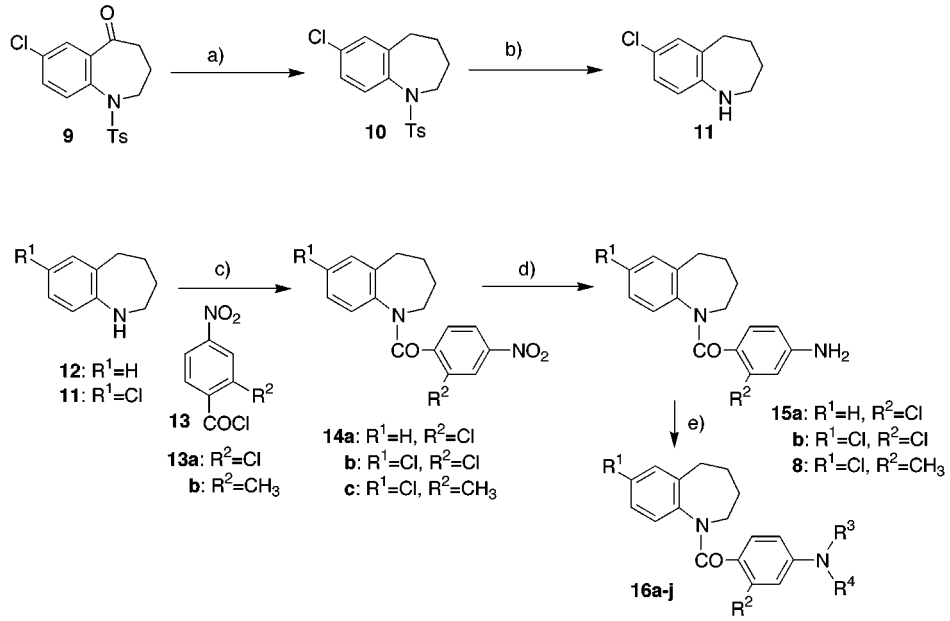
On the basis of the discovery of nonpeptide antagonists, we started to design a V_2 agonist by monitoring the accumulation of the cAMP production using human receptor expressed HeLa cells. During the early stage of our research to find the nonpeptide V_2 receptor antagonists, the phenoxyacetyl derivative **7** (Figure 2) showed an antidiuretic effect using Brattleboro rats by po administration (IC_{50} rat V_{1a} = 5.1 μM, V_2 = 0.038 μM; U.V. = 0 mL, 1 mg/kg, po).[10] As a result of the pharmacokinetic study for this series of compounds by po administration, we found that this phenoxyacetyl moiety of **7** was labile and easily transformed into aniline **8,** because the resulting aniline **8** and a trace amount of the parent compound were found in the blood serum. Though both compounds **7** and **8** showed a nanomolar magnitude of binding affinity to the human V_2 receptor (IC_{50} **7** = 0.95 nM, **8** = 4.1 nM), compound **7** did not show accumulation of cAMP while compound **8** showed a small amount of cAMP accumulation (9% at 10 μM). Compound **8** also showed an antidiuretic effect by po administration (U.V. = 3 mL, 1 mg/kg). As we have described in the finding for the potent V_2 receptor antagonist, the key to enhancing the binding affinity and selectivity is the position and nature of the functional groups at X and Y shown in Figure 2.[8b] After optimizing and evaluating the functional groups at X and Y, the requirement of an amino group on the phenyl ring using structure−activity relationships (SARs) led us to the discovery of novel nonpeptide V_2 receptor agonists. We also found an enhancement of agonist activity by adding functional groups to the lead compound **8**, but a narrow structural allowance was found for agonist activity on this series of compounds.

Chemistry

The syntheses of compound **8** and **16a**−**j** (Table 1) are shown in Scheme 1. 2,3,4,5-Tetrahydro-1*H*-1-benzazepine **(10)** was obtained by the Wolff−Kishner reduction of the 5-oxo derivative **9**. The 1-tosyl group was easily removed by the reaction with Mg in methanol to afford **11**. After the condensation of benzazepine **11** or **12** with 2-chloro-4-nitrobenzoyl chloride (**13a**) or 2-methyl-4-nitrobenzoyl chloride (**13b**), the nitro group of **14a**−**c** was reduced with $SnCl_2 \cdot 2H_2O$ to give the anilines **15a,b** and **8**, respectively. Target compounds (**16a**−**j**) were obtained by the alkylation of the aniline **15a,b** with the corresponding alkyl iodides in the presence of K_2CO_3 in DMF.

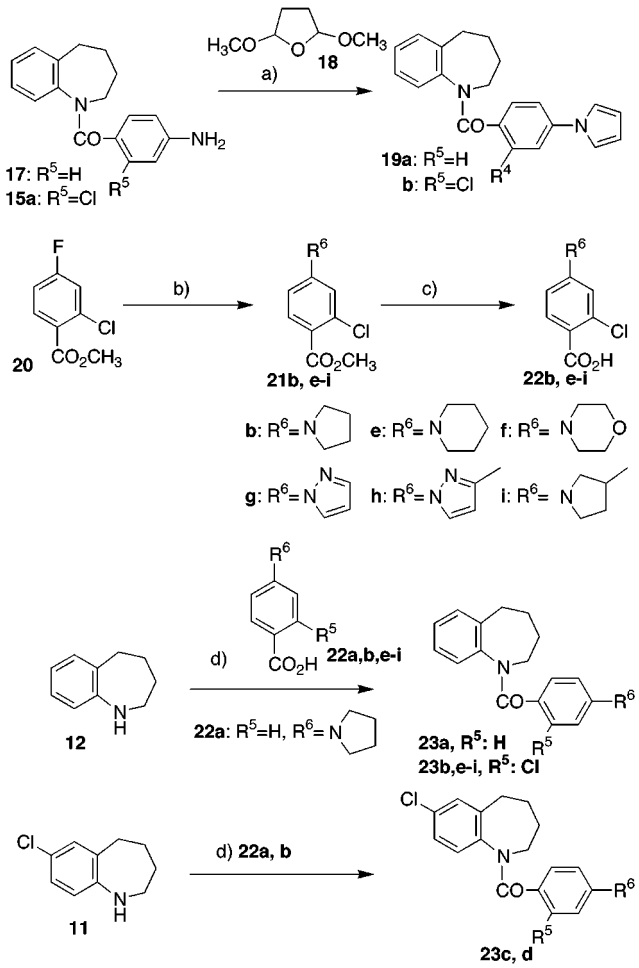
The synthesis of the heterocyclic ring-substituted derivatives (**19a,b, 23a**−**i**) is shown in Scheme 2. The

Scheme 1[a]



[a] Reagents: (a) hydrazine monohydrate, KOH, diethylene glycol; (b) Mg, MeOH; (c) pyridine, CH_2Cl_2; (d) $SnCl_2 \cdot 2H_2O$, EtOH; (e) R-I, K_2CO_3, DMF.

Scheme 2[a]



[a] Reagents: (a) AcOH; (b) R^6-H, K_2CO_3, NMP; (c) NaOH, MeOH; (d) (i) $SOCl_2$, NMP, CH_2Cl_2, (ii) pyridine, CH_2Cl_2.

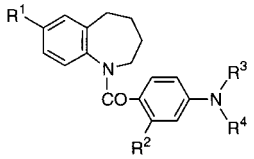
pyrrole derivatives **19a,b** were easily obtained from the anilines **17** and **15a** according to the Clauson−Kaas method[11] by heating with 2,5-dimethoxytetrahydrofuran (**18**) in acetic acid. The other heterocyclic ring-substituted benzoic acids were obtained by nucleophilic substitution of 4-F by the heterocyclic rings followed by hydrolysis of the ester groups. These benzoic acid derivatives thus obtained were condensed with the benzazepine derivatives **11** and **12** to afford the target compounds **23a**−**i**.

Results and Discussion

The SARs of R^1, R^2, and R^3 are shown in Table 1. The introduction of R^1 = Cl and R^2 = CH_3 (**8**) enhanced the binding affinity compared with the unsubstituted compound **17**. As we reported with the finding of compound **4** (Tolvaptan), the binding affinity of derivatives having R^2 = CH_3 was identical with R^2 = Cl; therefore, we have prepared the derivatives having R^2 = Cl by the commercial availability of the benzoyl chloride (**13a**). We were fortunate that only weak agonist activity of **8** and **16a** was observed as the accumulation of cAMP production, while unsubstituted compound **17** showed no cAMP accumulation. Agonist activity was enhanced when R^4 = CH_3 (**16b**), but the binding affinity was not affected. The diethylamino moiety (**16c**) or the introduction of a Cl group on R^1 (**16d**) did not enhance agonist activity. The monosubstituted amino derivatives are shown in **16e**−**j**. In this series of compounds, the *n*-propylamino derivative (**16g**) show the highest agonist activity. The ethylamino (**16e**), *n*-butylamino (**16h**), and *n*-pentylamino (**16i**) derivatives showed poor agonist activity compared with **16g**.

Molecular modeling was carried out to analyze the structural requirements of the amino moiety (P-1 region, Figure 3).[12] In comparison with the structures of **16b,c,g**, the P-1 region must be occupied with lipophilic substituents for the agonist activity. However, the steric requirements were rigorous at P-1, because the chain length and the size of the substituent were limited for the potency of agonist activity. Therefore, we designed

Table 1. Binding Affinity and Percentage of Maximal cAMP Accumulation for Aniline Derivatives



Compound	R^1	R^2	R^3	R^4	IC_{50} (μM)[a] (95% CI)	PMA (%)[b]
17[c]	H	H	H	H	0.18	0
8	Cl	CH_3	H	H	0.0041 (0.0036 - 0.0047)	9 ± 5.3 (10μM)
16a	H	Cl	CH_3	H	0.035 (0.025 - 0.049)	9.2 ± 0.9
16b	H	Cl	CH_3	CH_3	0.018 (0.012 - 0.026)	30 ± 1.2
16c	H	Cl	C_2H_5	C_2H_5	0.019 (0.014 - 0.026)	1.9 ± 0.3
16d	Cl	Cl	CH_3	CH_3	0.013 (0.012 - 0.015)	5.4 ± 0.8
16e	H	Cl	C_2H_5	H	0.034 (0.004 - 0.093)	12.6 ± 0.9
16f	Cl	Cl	C_2H_5	H	0.005 (0.001 - 0.018)	3.3 ± 0.5
16g	H	Cl	n-Pr	H	0.018 (0.012 - 0.026)	79.3 ± 4.9
16h	H	Cl	n-Bu	H	0.022 (0.014 - 0.034)	0
16i	H	Cl	n-Pent	H	0.031 (0.026 - 0.038)	2.1 ± 0.3
16j	H	Cl	Allyl	H	0.0059 (0.0050 - 0.0071)	19.9 ± 1.5

[a] Inhibition of [^{3}H]AVP binding to human V_2 receptor coded HeLa cells. IC_{50} values are the concentration of compound which inhibits [^{3}H]AVP binding by 50%. All assays were performed in duplicate. CI denotes confidence interval. [b] Percentage of maximal cAMP accumulation (PMA) at a concentration of 10^{-6} M. Values are means (%) ± SEM. [c] Reported in ref 5b.

the pyrrolidinyl derivative **23b** to fill the P-1 region. Also, **23i** was designed by the superimposition of **16g** and **23b** in order to show a more potent agonist activity.

Some heterocycle-substituted derivatives are shown in Table 2. As expected, **23b** showed potent agonist activity having the same order of binding affinity as **16b**. The substituent effects of the Cl atom at R^1 and R^5 are clearly understood by **23a**−**d**. The presence of the Cl atom at R^1 or the absence of the Cl atom at R^5 is obstructive for agonist activity. Interestingly, the binding affinity was strongly enhanced by introducing a Cl atom at R^5. This enhancement seems specific to the human receptor, because we have never observed this effect in the rat V_2 receptor in SAR of antagonists.[5,8] Six-membered rings at R^6 lower agonist activities more than the five-membered rings. More potent agonist activity was seen when a pyrrole ring was substituted at R^6 (**19a**) instead of pyrrolidine (**23a**), though the binding affinity was not satisfactory. Although the introduction of a Cl atom at R^5 (**19b**) enhances binding affinity, the accumulation of cAMP was moderate when compared with **19a**. The pyrazole derivative **23g** showed similar activities to **19b**, and the introduction of a 3-methyl group (**23h**) enhanced the activity. We were very happy to learn that the 3-methyl derivative **23i** possessed good affinity for the V_2 receptor and had potent agonist activity, as we had expected using molecular modeling.

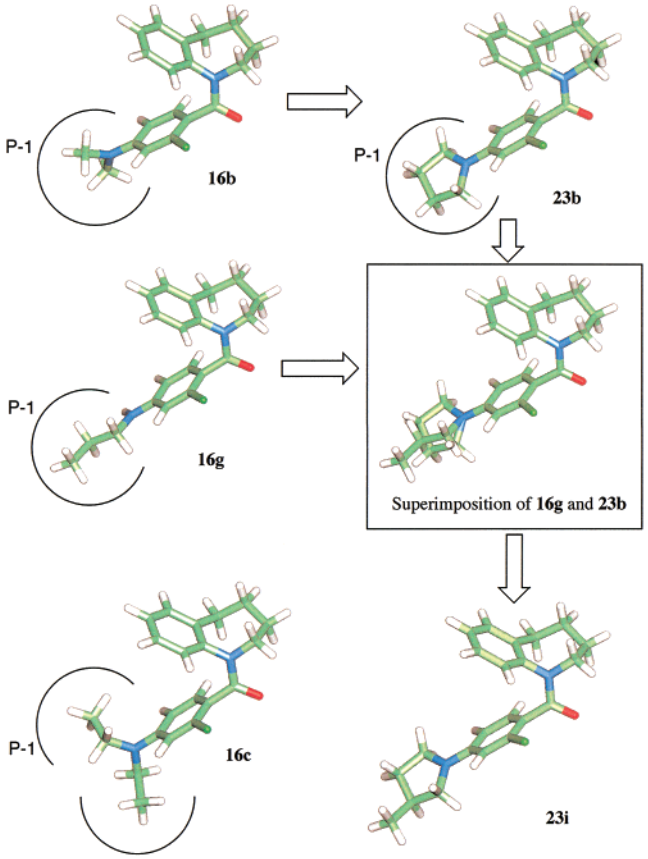


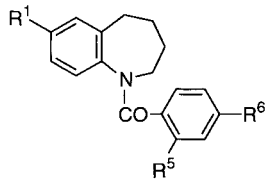
Figure 3. Schematic representations for P-1 regions shown as 3D models. Liquorice models are drawn using QUANTA97.

Figure 4 shows the concentration-dependent percentage of maximal cAMP accumulation for **16g, 19a,** and **23b,i. 19a** was shown to have high agonist activity at a concentration of 10^{-5} M. Other compounds seemed to be partial agonists. **23b** did not reach a maximum response at higher concentrations, but the binding affinity of **23b** is 9 nM (IC_{50}). There are also some gaps between the binding affinities (IC_{50}) and agonist activities at a concentration of 10^{-6} M for the other compounds, but the cAMP accumulation was observed at a low concentration when the compound showed high binding affinity like **23i**.

AVP V_2-receptor mediated cAMP accumulation of nonpeptide compound **23b** was confirmed by treating with V_2 receptor antagonist **3** (Figure 5), because the dose−response curve for cAMP accumulation of **23b** was shifted to the right by treating with the V_2 antagonist. And compound **23b** was not confirmed as a partial agonist by the interaction study with AVP (1 nM), because only a weak suppression was observed to the maximal cAMP accumulation. The antidiuretic effect of compound **23b** was also confirmed by po administration using Brattleboro rats (U.V. = 1.3 mL, 1 mg/kg), although the binding affinity of **23b** for the rat V_2 receptor was less potent than for the human receptor (IC_{50} rat V_2 = 0.15 μM).

The structural requirements responsible for binding affinity to the V_2 receptor and agonist activity are

Table 2. Binding Affinity and Percentage of Maximal cAMP Accumulation of Heterocyclic Derivatives



Compound	R^1	R^5	R^6	IC_{50} (μM)[a] (95% CI)	PMA (%)[b]
23a	H	H		1.0 (0.73 - 1.50)	47.6 ± 2.2
23b	H	Cl		0.009 (0.007 - 0.011)	64.5 ± 5.6
23c	Cl	H		0.21 (0.18 - 0.26)	25.2 ± 1.7
23d	Cl	Cl		0.016 (0.009 - 0.027)	23.2 ± 1.1
23e	H	Cl		0.12 (0.09 - 0.15)	8.3 ± 0.5
23f	H	Cl		N.D.	8.4 ± 3.2
19a	H	H		0.32 (0.20 - 0.52)	87.9 ± 10.7
19b	H	Cl		0.0075 (0.009 - 0.0208)	19.9 ± 1.2
23g	H	Cl		0.0088 (0.0039 - 0.0143)	12.9 ± 2.3
23h	H	Cl		0.013 (0.008 - 0.021)	68.3 ± 4.9
23i	H	Cl		0.051 (0.038 - 0.068)	73.2 ± 0.16

[a,b] See corresponding footnotes in Table 1.

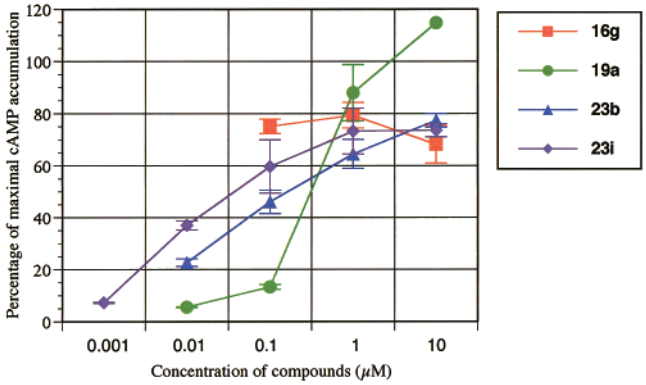


Figure 4. cAMP accumulation in response to nonpeptide compounds at the given concentration expressed as percent with standard error of the response obtained by stimulation with AVP (1 nM).

summarized in Figure 6. The steric size in the P-1 region is rigorously limited for revealing agonist activity. The P-2 region is important for enhancing binding affinity for the V_2 receptor. A substituent in the P-3 region lowers agonist activity.

Conclusion

The difference of only a single methyl group was shown to distinguish the agonist or antagonistic properties in the case of the nonpeptide angiotensin AT1 ligands.[9a−h] A very strict limitation was similarly found for the presence of agonist action using our ligands for the V_2 receptor in the P-1 region. We also found that the intensities of agonist action sharply fluctuated due to the difference of a single methylene group as shown in the case of **16g**,**h** or **23b**,**e**. These phenomena were easily understood by hypothesizing the presence of an activation cavity in the P-1 region. When this cavity is satisfied with a ligand, the maximam response of agonist action may be expected. The size of this cavity may be easily estimated using the superimposition of agonists shown in Figure 3.

We believe that our evaluation of the structural requirements for the P-1, P-2, and P-3 regions may be useful for understanding the signal transduction mechanisms inside the receptor.

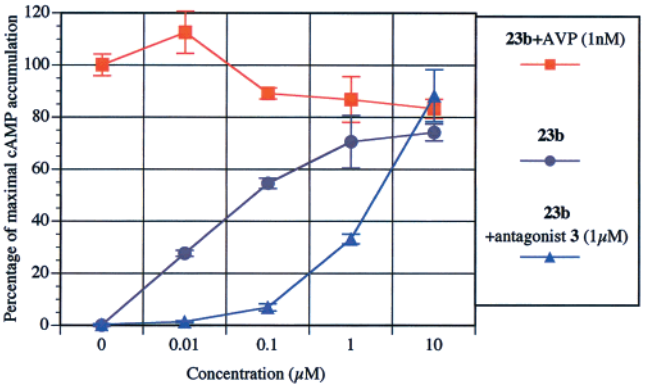


Figure 5. cAMP accumulation in response to nonpeptide compounds (**23b**) treated alone or with AVP (1 nM) or V_2 antagonist **3** (1 μM) in human V_2 receptor transfected HeLa cells. The cAMP accumulation is expressed as percentage with standard error of the maximal response obtained by stimulation with AVP (1 nM).

Experimental Section

Melting points were determined using a Yanagimoto micro point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on Bruker AC-200 (200 MHz) or DPX-300 (300 MHz) spectrometers using tetramethylsilane (TMS) or 3-(trimethylsilyl)propionic acid-d_5 (TSP) as the internal standard. Some of the integral values and peaks were not well determined due to the broadening of the peaks by the slow exchange of rotamers. Elemental analyses were determined with a Yanaco MT-5 CHN recorder. Mass spectra were measured on a Varian MAT-312 instrument. All compounds were routinely checked by TLC on Merck silica gel 60 F_{254} precoated plates. Chromatography refers to flash chromatography using a E. Merck Kieselgel 60, 230−400 mesh silica gel. All materials were commercially available unless otherwise noted.

7-Chloro-1-toluenesulfonyl-1,2,3,4-tetrahydro-1*H*-1-benzazepine (10). A mixture of ketone **9** (50 g, 0.143 mol), hydrazine monohydrate (29 mL, 0.60 mol) and KOH (37.8 g, 0.95 mol) in diethylene glycol (500 mL) was heated at reflux for 6 h. After cooling, the reaction mixture was poured into ice−water and the pH was adjusted to 7 by adding 1 N HCl, then extracted with AcOEt. The organic layers were separated, washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting precipitates were crystallized with Et_2O to give **10** (44.6 g, 93%) as a white powder: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.43−1.91 (4H, m), 2.22−2.47 (2H, m), 2.42 (3H, s), 3.41−3.93 (2H, m), 7.05−7.35 (5H, m), 7.52−7.67 (2H, m).

7-Chloro-1,2,3,4-tetrahydro-1*H*-1-benzazepine (11). To a solution of tosylate **10** (30 g, mmol) in MeOH (300 mL) was

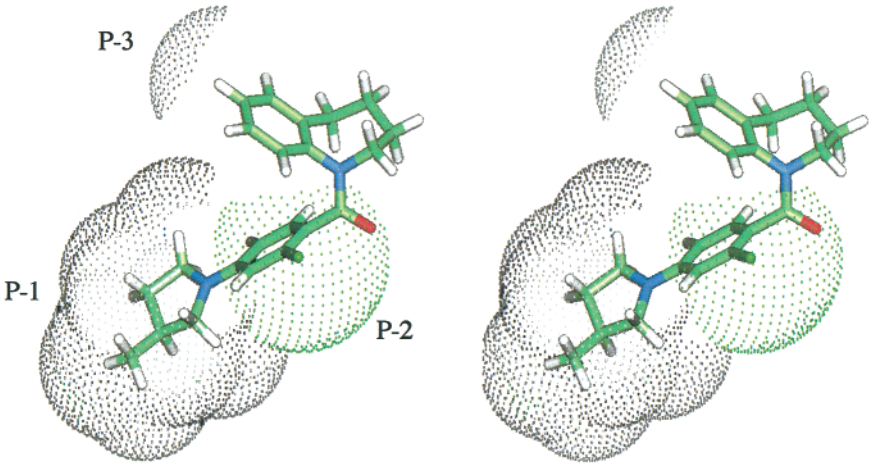


Figure 6. Stereo 3D plot of **23i**. Solvent-accessible surface areas of P-1, P-2, and P-3 regions are shown as dotted spheres.

slowly added Mg (7.2 g, mmol) to maintain a gentle reflux and H_2 evolution. After stirring for 4 h at ambient temperature, the mixture was concentrated under reduced pressure. The resulting precipitates were dispersed with CH_2Cl_2, then dilute aqueous NaOH was slowly added to dissolve the precipitates with ice cooling. The organic layer was separated, washed with water, dried over $MgSO_4$, and concentrated to afford **11** (11.1 g, quant.) as a pale yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.47−1.93 (4H, m), 2.62−4.03 (5H, m), 6.63 (1H, d, J = 8.3 Hz), 6.97 (1H, dd, J = 8.3, 2.4 Hz), 7.07 (1H, d, J = 2.4 Hz).

(1,2,3,4-Tetrahydro-1*H*-1-benzazepin-1-yl)-2-chloro-4-nitrobenzamide (14a). To a mixture of **12** (5 g, 34 mmol), pyridine (13.7 mL, 170 mmol) in CH_2Cl_2 (500 mL) was added dropwise a solution of 2-chloro-4-nitrobenzoyl chloride (**13a**; 9 g, 40.8 mmol) in CH_2Cl_2 (10 mL) at 0−5 °C. After stirring for 1 h, the mixture was poured into water, and extracted with CH_2Cl_2. The organic layers were separated, washed with dilute HCl, water, dried over Na_2CO_3 and concentrated. The residue was purified by silica gel column chromatography (*n*-hexane:AcOEt, 5:1), and crystallized with *i*-Pr_2O to give **14a** (7.72 g, 69%) as a white powder: mp 114−115 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38−2.21 (4H, m), 2.83−3.72 (3.1H, m), 4.82−4.95 (0.9H, m), 6.83−7.43 (5.2H, m), 7.86−7.94 (0.9H, m), 8.08−8.18 (0.9H, m).

(7-Chloro-1,2,3,4-tetrahydro-1*H*-1-benzazepin-1-yl)-2-chloro-4-nitrobenzamide (14b). Using the same procedure as **14a, 14b** (7.69 g, 77%) was obtained as a white powder from **11** (5 g, 27.5 mmol): mp 129−130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33−2.28 (4H, m), 2.58−3.63 (3.1H, m), 4.78−4.98 (0.9H, m), 6.75−7.36 (4.2H, m), 7.93 (0.9H, d, J = 7.7 Hz), 8.16 (0.9H, s).

(7-Chloro-1,2,3,4-tetrahydro-1*H*-1-benzazepin-1-yl)-2-methyl-4-nitrobenzamide (14c). Using the same procedure as **14a, 14c** (1.73 g, 91%) was obtained as a white powder from **11** (1 g, 5.5 mmol) and 2-methyl-4-nitrobenzoyl chloride (**13b**; 1.2 g, 6.6 mmol):[8b] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38−2.28 (4H, m), 2.53, 2.59 (total 3H, each s), 2.63−3.55 (3.1H, m), 4.33−5.06 (0.9H, m), 6.55 (1H, d, J = 8.3 Hz), 6.85 (1H, dd, J = 8.3, 2.4 Hz), 6.93 (0.9H, d, J = 8.4 Hz), 7.17 (1H, d, J = 2.4 Hz), 7.49−7.62 (0.1H, m), 7.77 (0.9H, dd, J = 8.4, 2.2 Hz), 8.00 (0.9H, d, J = 2.2 Hz), 8.07−8.25 (0.2H, m).

(1,2,3,4-Tetrahydro-1*H*-1-benzazepin-1-yl)-4-amino-2-chlorobenzamide (15a). A mixture of **14a** (7.72 g, 23.3 mmol) and $SnCl_2 \cdot 2H_2O$ (26.3 g, 117 mmol) in EtOH (200 mL) was heated under reflux for 3 h. After cooling to ambient temperature, the mixture was concentrated under reduced pressure. The residue thus obtained was dispersed in CH_2Cl_2 and aqueous 6 N NaOH was slowly added to dissolve some precipitated materials. After the extraction with CH_2Cl_2, the organic layers were separated, washed with water, dried over Na_2CO_3, and concentrated. The resulting crystals were washed with Et_2O to yield **15a** (6.7 g, 86%) as a white powder: mp 187−189 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32−2.28 (4H, m), 2.65−4.08 (5.2H, m), 4.83−5.03 (0.8H, m), 6.23 (0.8H, dd, J = 8.3, 2.2 Hz), 6.54 (0.8H, d, J = 2.2 Hz), 6.56−7.43 (5.4H, m).

(7-Chloro-1,2,3,4-tetrahydro-1*H*-1-benzazepin-1-yl)-4-amino-2-chlorobenzamide (15b). Using the same procedure as **15a, 15b** (5.3 g, 84%) was obtained as a white powder from **14b** (7.69 g, 21.1 mmol): mp 196−198 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33−2.17 (4H, m), 2.45−4.02 (5.15H, m), 4.79−4.98 (0.85H, m), 6.27 (0.85H, dd, J = 8.3, 2.2 Hz), 6.54 (0.85H, d, J = 2.2 Hz), 6.68−6.85 (1.1H, m), 6.81 (0.85H, dd, J = 8.4, 2.3 Hz), 7.12 (0.85H, d, J = 2.3 Hz, 7.15−7.33 (0.65H, m).

(7-Chloro-1,2,3,4-tetrahydro-1*H*-1-benzazepin-1-yl)-4-amino-2-methylbenzamide (8). Using the same procedure as **15a, 8** (1.52 g, 97%) was obtained as a white powder from **14c** (1.71 g, 5.0 mmol): mp 199−200 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30−2.18 (4H, m), 2.34 (3H, s), 2.45−3.93 (5.1H, m), 4.75−5.13 (0.9H, m), 6.07−6.23 (0.9H, m), 6.33−6.67 (3.1H, m), 6.77−6.93 (1H, m), 7.06−7.27 (1H, m). Anal. ($C_{18}H_{19}ClN_2O$) C, H, N.

(1,2,3,4-Tetrahydro-1*H*-1-benzazepin-1-yl)-2-chloro-4-(*N*-methylamino)benzamide (14a) and (1,2,3,4-Tetrahydro-1*H*-1-benzazepin-1-yl)-2-chloro-4-(*N*,*N*-dimethylamino)-benzamide (16b). A mixture of **15a** (1 g, 3.3 mmol), MeI (0.41 mL, 6.6 mmol), K_2CO_3 (0.68 g, 5 mmol) in DMF (50 mL) was heated at 70 °C for 1 day. The reaction mixture was poured into water, extracted with AcOEt−toluene, washed three times with water, dried over Na_2CO_3 and concentrated. The resulting precipitates were purified by silica gel column chromatography (*n*-hexane:AcOEt, 4:1) followed by recrystallization from MeOH−CH_2Cl_2 to give **16a** (TLC R_f ca. 0.3, *n*-hexane:AcOEt 2:1, 0.2 g, 19%) as a white powder: mp 203−204 °C; ^{1}H NMR (300 MHz, CDCl3) δ 1.32−2.18 (4H, m), 2.61−4.12 (7.15H, m), 4.83−5.03 (0.85H, m), 6.14 (0.85H, dd, J = 8.4, 2.3 Hz), 6.43 (0.85H, d, J = 2.3 Hz), 6.48−6.65 (0.3H, m), 6.70 (0.85H, d, J = 8.4 Hz), 6.82−7.43 (4.15H, m). Anal. ($C_{18}H_{19}N_2OCl$) C, H, N. **16b** (TLC R_f ca. 0.7, *n*-hexane:AcOEt 2:1, 0.55 g, 51%) as colorless prisms: mp 173−174 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32−2.26 (4H, m), 2.52−3.87 (9.15H, m), 4.83−5.05 (0.85H, m), 6.24 (0.85H, dd, J = 8.7, 2.5 Hz), 6.51 (0.85H, d, J = 2.5 Hz), 6.59−6.83 (1.1H, m), 6.85−7.44 (4.2H, m). Anal. ($C_{19}H_{21}N_2$-OCl) C, H, N.

(1,2,3,4-Tetrahydro-1*H*-1-benzazepin-1-yl)-2-chloro-4-(*N*,*N*-diethylamino)benzamide (16c) and (1,2,3,4-Tetrahydro-1*H*-1-benzazepin-1-yl)-2-chloro-4-(*N*-ethylamino)benzamide (16e). Using the same procedure as **16b**, the diethylamino derivative (**16c**, TLC R_f ca. 0.7, *n*-hexane:AcOEt, 2:1, 0.3 g, 26%) was obtained as colorless prisms from **15a** (1 g, 3.3 mmol) using EtI (0.8 mL, 10 mmol) instead of MeI in *N*-methyl-2-pyrrolidone (NMP): mp 162−163.5 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.88−2.24 (0.3H, m), 2.52−3.55 (7.2H, m), 4.80−5.13 (0.8H, m), 6.20 (0.8H, dd, J = 8.7, 2.5 Hz), 6.30−7.44 (6.2H, m). Anal. ($C_{21}H_{25}N_2OCl$) C, H, N. Monoethylamino derivative **16e** (TLC R_f ca. 0.4, *n*-hexane:AcOEt, 2:1, 0.55 g, 52%) was obtained as colorless prisms: mp 180−182 °C; ^{1}H NMR (200

MHz, $CDCl_3$) δ 1.17, 1.27 (total 3H, each t, J = 7.2 Hz), 1.33−2.23 (4H, m), 2.55−4.45 (6.2H, m), 4.83−5.04 (0.8H, m), 6.14 (0.8H, dd, J = 8.4, 2.3 Hz), 6.23−7.43 (6.2H, m). Anal. ($C_{19}H_{21}N_2OCl \cdot 0.2H_2O$) C, H, N.

(7-Chloro-1,2,3,4-tetrahydro-1*H*-1-benzazepin-1-yl)-2-chloro-4-(*N*,*N*-dimethylamino)benzamide (16d). Using the same procedure as **16b**, the dimethylamino derivative **16d** (TLC R_f ca. 0.7, *n*-hexane:AcOEt, 2:1, 0.35 g, 32%) was obtained as a white powder from **15b** (1 g, 3 mmol): mp 172−173 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30−2.18 (4H, m), 2.43−3.83 (9.15H, m), 4.80−5.03 (0.85H, m), 6.28 (0.85H, dd, J = 8.6, 2.4 Hz), 6.51 (0.85 H, d, J = 2.4 Hz), 6.56−7.43 (4.3 H, m). Anal. ($C_{19}H_{20}N_2OCl_2$) C, H, N. (7-Chloro-1,2,3,4-tetrahydro-1*H*-1-benzazepin-1-yl)-2-chloro-4-(*N*-methylamino)benzamide (TCL R_f ca. 0.4, *n*-hexane:AcOEt, 2:1, 0.21 g, 20%) was obtained as a white powder: mp 150−151 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29−2.18 (4H, m), 2.47−4.13 (7.1H, m), 4.80−5.03 (0.9H, m), 6.18 (0.9H, dd, J = 8.4, 2.0 Hz), 6.43 (0.9H, d, J = 2.0 Hz), 6.47−6.97 (2.9H, m), 7.05−7.37 (1.3H, m).

(7-Chloro-1,2,3,4-tetrahydro-1*H*-1-benzazepin-1-yl)-2-chloro-4-(*N*-ethylamino)benzamide (16f). Using the same procedure as **16a**, the ethylamino derivative **16f** (TLC R_f ca. 0.4, *n*-hexane:AcOEt, 2:1, 0.77 g, 74%) was obtained as colorless prisms from **15b** (1 g, 2.88 mmol) using EtI (0.7 mL, 8.6 mmol) instead of MeI: mp 160−162 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20, 1.28 (total 3H, each t, J = 7.1 Hz), 1.33−2.18 (4H, m), 2.60−4.03 (6.15H, m), 4.82−5.03 (0.85H, m), 6.18 (0.85H, dd, J = 8.4, 2.2 Hz), 6.43 (0.85H, d, J = 2.2 Hz), 6.56−6.63 (0.3H, m), 6.69 (0.85H, d, J = 8.4 Hz), 6.81 (0.85H, d, J = 8.4 Hz), 6.89 (0.85H, dd, J = 8.4, 2.3 Hz), 7.12 (0.85H, d, J = 2.3 Hz), 7.15−7.36 (0.6H, m). Anal. ($C_{19}H_{20}N_2OCl_2$) C, H, N. Diethylamino derivative (TLC R_f ca. 0.7, *n*-hexane:AcOEt, 2:1, 0.12 g, 10%) was obtained as a white powder: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97−2.23 (10H, m), 2.53−3.78 (7.15H, m), 4.83−5.07 (0.85H, m), 6.23 (0.85H, dd, J = 8.7, 2.4 Hz) 6.47 (0.85H, d, J = 2.4 Hz), 6.53−6.75 (1.15H, m), 6.82 (0.85H, d, J = 8.4 Hz), 6.90 (0.85H, dd, J = 8.4, 2.3 Hz), 7.06−7.38 (1.45H, m).

(1,2,3,4-Tetrahydro-1*H*-1-benzazepin-1-yl)-2-chloro-4-(*N*-*n*-propylamino)benzamide (16g). Using the same procedure as **16a**, the *n*-propylamino derivative **16g** (TLC R_f ca. 0.4, *n*-hexane:AcOEt, 2:1, 0.9 g, 80%) was obtained as a white powder from **15a** (1 g, 3.3 mmol) using *n*-propyl iodide instead of MeI: mp 139−141 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93, 1.01 (total 3H, each t, J = 7.4 Hz), 1.32−2.20 (6H, m), 3.66−4.08 (6.15H, m), 4.85−5.03 (0.85H, m), 6.14 (0.85H, dd, J = 8.4, 2.3 Hz), 6.43 (0.85H, d, J = 2.3 Hz), 6.45−7.44 (5.3H, m). Anal. ($C_{20}H_{23}N_2OCl$) C, H, N. (1,2,3,4-Tetrahydro-1*H*-1-benzazepin-1-yl)-2-chloro-4-(*N*,*N*-di-*n*-propylamino)benzamide (TLC R_f ca. 0.7, *n*-hexane:AcOEt, 2:1, 0.1 g, 8%) was obtained as a white powder: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86, 0.95 (total 6H, each t, J = 7.4 Hz), 1.33−2.21 (8H, m), 2.48−3.77 (7.2H, m), 4.85−5.06 (0.8H, m), 6.16 (0.8H, dd, J = 8.7, 2.4 Hz), 6.24 (0.8H, d, J = 2.4 Hz), 6.48−6.75 (1.2H, m), 6.84−7.43 (4.2H, m).

(1,2,3,4-Tetrahydro-1*H*-1-benzazepin-1-yl)-2-chloro-4-(*N*-*n*-butylamino)benzamide (16h). Using the same procedure as **16a**, the *n*-butylamino derivative **16h** (TLC R_f ca. 0.4, *n*-hexane:AcOEt, 2:1, 0.8 g, 68%) was obtained as a white powder from **15a** (1 g, 3.3 mmol) using *n*-butyl iodide instead of MeI: mp 137−139 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92, 0.97 (total 3H, each t, J = 7.2 Hz), 1.25−2.16 (8H, m), 2.67−3.94 (6.1H, m), 4.86−5.02 (0.9H, m), 6.13 (0.9H, dd, J = 8.4, 2.3 Hz), 6.43 (0.9H, d, J = 2.3 Hz), 6.50−7.42 (5.2H, m). Anal. ($C_{21}H_{25}N_2OCl$) C, H, N. (1,2,3,4-Tetrahydro-1*H*-1-benzazepin-1-yl)-2-chloro-4-(*N*,*N*-di-*n*-butylamino)benzamide (TLC R_f ca. 0.7, *n*-hexane:AcOEt, 2:1, 0.1 g, 7%) was obtained as a white powder: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91, 0.97 (total 6H, each t, J = 7.2 Hz), 1.03−2.16 (12H, m), 2.55−3.85 (7.2H, m), 4.85−5.07 (0.8H, m), 6.16 (0.8H, dd, J = 8.7, 2.4 Hz), 6.43 (0.8H, d, J = 2.4 Hz), 6.48−6.74 (1.1H, m), 6.82−7.43 (4.3H, m).

(1,2,3,4-Tetrahydro-1*H*-1-benzazepin-1-yl)-2-chloro-4-(*N*-*n*-pentylamino)benzamide (16i). Using the same procedure as **16a**, the *n*-pentylamino derivative **16i** (TLC R_f ca. 0.4, *n*-hexane:AcOEt, 2:1, 0.6 g, 49%) was obtained as a white powder from **15a** (1 g, 3.3 mmol) using *n*-butyl iodide instead of MeI: mp 124−125 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.78−1.00 (3H, m), 1.21−2.27 (0.3H, m), 2.62−4.06 (6.15H, m), 4.82−5.08 (0.85H, m), 6.13 (0.85H, dd, J = 8.4, 2.3 Hz), 6.42 (0.85H, d, J = 2.3 Hz), 6.48−6.73 (1.15H, m), 6.86−7.42 (4.15H, m). Anal. ($C_{22}H_{27}N_2OCl$) C, H, N.

(1,2,3,4-Tetrahydro-1*H*-1-benzazepin-1-yl)-2-chloro-4-(*N*-allylamino)benzamide (16j). Using the same procedure as **16a**, the *n*-allylamino derivative **16j** (TLC R_f ca. 0.4, *n*-hexane:AcOEt, 2:1, 0.49 g, 62%) was obtained as a white powder from **15a** (0.7 g, 2.3 mmol) using the allyl bromide instead of MeI: mp 130−133 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34−2.28 (4H, m), 2.60−4.22 (6.15H, m), 4.82−5.05 (0.85H, m), 5.05−5.39 (2H, m), 5.63−6.00 (1H, m), 6.16 (0.85H, dd, J = 8.4, 2.2 Hz), 6.45 (0.85H, d, J = 2.2 Hz), 6.52−6.59 (0.15H, m), 6.60−6.75 (1H, m), 6.84−6.97 (1.7H, m), 7.02 (0.85H, dt, J = 1.7, 7.1 Hz), 7.12 (0.85H, d, J = 7.2 Hz), 7.16−7.33 (0.6H, m), 7.34−7.45 (0.15H, m). Anal. ($C_{20}H_{21}N_2OCl$) C, H, N.

(1,2,3,4-Tetrahydro-1*H*-1-benzazepin-1-yl)-4-(pyrrol-1-yl)benzamide (19a). A mixture of **17** (2 g, 5.5 mmol) and 2,5-dimethoxytetrahydrofuran **(18)** (1.02 mL, 7.9 mmol) in AcOH (10 mL) was heated at reflux for 15 min. After the reaction was completed, the mixture was concentrated under reduced pressure. The residue was dissolved in AcOEt, washed with dilute aqueous NaOH, water, dried over Na_2CO_3, and concentrated. The residue was purified by silica gel column chromatography (*n*-hexane:AcOEt 4:1) and recrystallized with AcOEt:*n*-hexane to give **19a** (1.2 g, 50%) as colorless columns: mp 159−160 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.85−2.23 (3H, m), 2.67−3.18 (3H, m), 4.94−5.12 (1H, m), 6.27−6.33 (2H, m), 6.66 (1H, d, J = 8.0 Hz), 6.88−7.28 (9H, m). Anal. ($C_{21}H_{20}N_2O$) C, H, N.

(1,2,3,4-Tetrahydro-1*H*-1-benzazepin-1-yl)-2-chloro-4-(pyrrol-1-yl)benzamide (19b). Using the same procedure as **19a, 19b** (0.69 g, 84%) was obtained as a white powder from **15a** (0.7 g, 2.3 mmol): mp 155−156 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.31−2.25 (4H, m), 2.67−3.73 (3.1H, m), 4.83−5.02 (0.9H, m), 6.21−6.43 (2H, m), 6.83−7.57 (9H, m). Anal. ($C_{21}H_{19}N_2OCl$) C, H, N.

2-Chloro-4-(pyrrolidin-1-yl)benzoic Acid Methyl Ester (21b). A mixture of 2-chloro-4-fluorobenzoic acid methyl ester **(20)** (2 g, 10.6 mmol), pyrrolidine (0.91 g, 12.8 mmol),and K_2CO_3 (2.9 g, 21 mmol) in *N*-methyl-2-pyrrolidone (10 mL) was heated at 120 °C for 5 h. After cooling to ambient temperature, the mixture was poured into water, extracted with AcOEt, washed with water, dried over $MgSO_4$, and concentrated. The resulting precipitates were washed with Et_2O to give **21b** (1.9 g, 76%) as yellow prisms: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.90−2.16 (4H, m), 3.21−3.45 (4H, m), 3.85 (3H, s), 6.38 (1H, dd, J = 8.9, 2.5 Hz), 6.52 (1H, d, J = 2.5 Hz), 7.83 (1H, d, J = 8.9 Hz).

2-Chloro-4-(piperidin-1-yl)benzoic Acid Methyl Ester (21e). Using the same procedure as **21b**, **21e** (1.3 g, 88%) was obtained as a white powder from **20** (1.1 g, 5.8 mmol) using piperidine instead of pyrrolidine: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.54−1.80 (6H, m), 3.20−3.41 (4H, m), 3.86 (3H, s), 6.71 (1H, dd, J = 8.9, 2.6 Hz), 6.84 (1H, d, J = 2.6 Hz), 7.82 (1H, d, J = 8.9 Hz).

2-Chloro-4-(morpholin-4-yl)benzoic Acid Methyl Ester (21f). Using the same procedure as **21b, 21f** (6.6 g, 78%) was obtained as colorless needles from **20** (6.2 g, 32.9 mmol) using morpholine instead of pyrrolidine: ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.19−3.38 (4H, m), 3.77−3.97 (4H, m), 3.87 (3H, s), 6.73 (1H, dd, J = 8.9, 2.6 Hz), 6.86 (1H, d, J = 2.6 Hz), 7.86 (1H, d, J = 8.9 Hz).

2-Chloro-4-(pyrazol-1-yl)benzoic Acid Methyl Ester (21g). Using the same procedure as **21b**, **21g** (16 g, 85%) was obtained as a white powder from **20** (15 g, 79.5 mmol) using pyrazole instead of pyrrolidine: ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.95 (3H, s), 6.48−6.58 (1H, m), 7.66 (1H, dd, J = 8.6, 2.2 Hz), 7.73−7.79 (1H, m), 7.93−8.03 (2H, m).

2-Chloro-4-(3-methylpyrazol-1-yl)benzoic Acid Methyl Ester (21h). Using the same procedure as **21b, 21h** (12.1 g,

61%, as less polar product) was obtained as a white powder from **20** (15 g, 79.5 mmol) using 3-methylpyrazole instead of pyrrolidine: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.38 (3H, s), 3.94 (3H, s), 6.30 (1H, d, J = 2.5 Hz), 7.59 (1H, dd, J = 8.6, 2.2 Hz), 7.82 (1H, d, J = 2.2 Hz), 7.86 (1H, d, J = 2.5 Hz), 7.96 (1H, d, J = 8.6 Hz). 2-Chloro-4-(5-methylpyrazol-1-yl)benzoic acid methyl ester (2.1 g, 11%, as polar product) was obtained as a white powder: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.44 (3H, s), 3.96 (3H, s), 6.22−6.25 (1H, m), 7.47 (1H, dd, J = 8.4, 2.1 Hz), 7.68−7.62 (1H, m), 7.66 (1H, d, J = 2.1 Hz), 7.97 (1H, d, J = 8.4 Hz).

2-Chloro-4-(pyrrolidin-1-yl)benzoic Acid (22b). A mixture of **21b** (1 g, 4.2 mmol), 5 N NaOH (2 mL) in MeOH (5 mL) was heated at reflux for 15 h. After the reaction was completed, 2 N HCl was added to adjust the pH to ca. 5, then concentrated under reduced pressure. The resulting precipitates were dispersed in MeOH−CH_2Cl_2, and any undissolved materials were removed by filtration. The filtrates were concentrated, washed with MeOH, then dried to afford **22b** (0.5 g, 53%) as a white powder: ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.76−2.02 (4H, m), 3.11−3.46 (4H, m), 6.34−6.63 (2H, m), 7.75 (1H, d, J = 8.6 Hz), 12.35 (1H, brs).

2-Chloro-4-(piperidin-1-yl)benzoic Acid (22e). Using the same procedure as **22b, 22e** (0.74 g, 60%) was obtained as a white powder from **15e** (1.3 g, 5.1 mmol): ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.45−1.73 (6H, m), 3.21−3.48 (4H, m), 6.88−7.12 (2H, m), 7.74 (1H, d, J = 8.7 Hz), 8.60 (1H, brs).

2-Chloro-4-(morpholin-4-yl)benzoic Acid (22f). Using the same procedure as **22b, 22f** (0.92 g, 98%) was obtained as a white powder from **21f** (1 g, 3.9 mmol): ^{1}H NMR (200 MHz, DMSO-d_6) δ 3.15−3.37 (4H, m), 3.60−3.80 (4H, m), 6.79−7.05 (2H, m), 7.75 (1H, d, J = 8.7 Hz). The corresponding COOH proton was not observed under this condition.

2-Chloro-4-(pyrazol-1-yl)benzoic Acid (22g). A mixture of **22g** (10 g, 42.3 mmol), 6 N HCl (10 mL) and AcOH (10 mL) was heated at reflux for 4 h. After the reaction was completed, the mixture was poured into ice−water, and the resulting crystals were collected by filtration to provide **22g** (9.6 g, 100%) as a white powder.

2-Chloro-4-(3-methylpyrazol-1-yl)benzoic Acid (22h). Using the same procedure as **22g**, **22h** (11 g, 97%) was obtained as a white powder from **21h** (12 g, 48 mmol): ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.28 (3H, s), 6.41 (1H, d, J = 2.4 Hz), 7.80−8.06 (3H, m), 8.55 (1H, d, J = 2.6 Hz), 13.3 (1H, brs).

3-Methylpyrrolidine. To a dispersion of $LiAlH_4$ (9.6 g, 0.252 mol) in Et_2O (200 mL) was added dropwise a solution of 3-methyl-2-pyrrolidone (25 g, 0.252 mol) in Et_2O (100 mL) at 0−5 °C. After completing the additions, the mixture was heated at reflux for 1h. The mixture was then cooled to 0−5 °C, and saturated aqueous Na_2SO_4 was added dropwise until the generation of H_2 gas had ceased. After additional stirring for 30 min at 0−5 °C, the resulting precipitates were removed by filtration. The filtrates were concentrated to give 3-methylpyrrolidine (18 g, 84%) as a yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.91 (3H, d, J = 6.6 Hz), 1.04−1.28 (1H, m), 1.68−2.11 (2H, m), 2.27 (1H, dd, J = 10.6, 7.1 Hz), 2.68−3.02 (3H, m), 4.71 (1H, brs).

2-Chloro-4-(3-methylpyrrolidin-1-yl)benzoic Acid (22i). A mixture of **20** (10 g, 53 mmol), 3-methylpyrrolidine (5.4 g, 63 mmol), and K_2CO_3 (63 mmol) in NMP (20 mL) was heated at 120 °C for 4 h. After cooling, the mixture was poured into water, extracted with AcOEt, washed with water, dried over $MgSO_4$, and concentrated. The residue thus obtained was diluted with MeOH (50 mL), and 6 N NaOH (21 mL) was then added to the mixture. After refluxing for 1 h, yellow cakes resulted. The cakes were dissolved in water, the pH was adjusted to ca. 4 by adding concentrated HCl, extracted with AcOEt, dried over $MgSO_4$, and concentrated. The precipitates were washed with i-Pr_2O to afford **22i** (9 g, 71%) as a pale brown powder: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.14 (3H, d, J = 6.6 Hz), 1.51−1.77 (1H, m), 1.96−2.54 (2H, m), 2.80−2.98 (1H, m), 3.18−3.58 (3H, m), 6.38 (1H, dd, J = 8.9, 2.4 Hz), 6.52 (1H, d, J = 2.4 Hz), 7.97 (1H, d, J = 8.7 Hz), 8.90 (1H, brs).

(1,2,3,4-Tetrahydro-1*H*-1-benzazepin-1-yl)-4-(pyrrolidin-1-yl)benzamide (23a). A mixture of 4-pyrrolidin-1-ylbenzoic acid **(22a)**[13] (2.85 g, 14.9 mmol), $SOCl_2$ (1.2 mL, 16.3 mmol), and NMP (2 drops) in CH_2Cl_2 (50 mL) was stirred overnight at room temperature to prepare the acid chloride solution. To a mixture of **12** (2 g, 13.6 mmol) and pyridine (5.5 mL, 68 mmol) in CH_2Cl_2 (100 mL) was added dropwise a solution of the acid chloride at 0−5 °C. After stirring for 3 h at room temperature, the mixture was poured into water, extracted with CH_2Cl_2, washed with water, dried over Na_2CO_3, and concentrated. The resulting residue was purified by silica gel column chromatography (*n*-hexane:AcOEt, 4:1) to give **23a** (2.3 g, 52%) as colorless prisms: mp 182−183 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.30−2.15 (6H, m), 2.50−3.45 (5H, m), 4.82−5.31 (1H, m), 6.15−6.30 (2H, m), 6.65−6.77 (1H, m), 6.85−7.28 (5H, m). Anal. ($C_{21}H_{24}N_2O$) C, H, N.

(1,2,3,4-Tetrahydro-1*H*-1-benzazepin-1-yl)-2-chloro-4-(pyrrolidin-1-yl)benzamide (23b). Using the same procedure as **23a**, **23b** (0.3 g, 39%) was obtained as a white powder from **12** (0.32 g, 2.2 mmol) and **22b** (0.5 g, 2.2 mmol): mp 160−162 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.27−2.20 (8H, m), 2.60−3.58 (7.1H, m), 4.83−5.12 (0.9H, m), 6.08 (0.9H, dd, J = 8.5, 2.2 Hz), 6.31−6.63 (1.3H, m), 6.72 (0.9H, d, J = 8.5 Hz), 6.82−7.45 (3.9H, m). Anal. ($C_{21}H_{23}N_2OCl$) C, H, N.

(7-Chloro-1,2,3,4-tetrahydro-1*H*-1-benzazepin-1-yl)-4-(pyrrolidin-1-yl)benzamide (23c). Using the same procedure as **23a, 23c** (1.8 g, 46%) was obtained as colorless needles from **11** (2 g, 11 mmol) and **22a** (2.3 g, 12 mmol): mp 147−148 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.32−2.17 (6H, m), 2.47−3.34 (5H, m), 4.70−5.33 (1H, m), 6.20−6.32 (2H, m), 6.63 (1H, d, J = 8.4 Hz), 6.92 (1H, dd, J = 8.4, 2.4 Hz), 7.03−7.14 (2H, m), 7.22 (1H, d, J = 2.4 Hz). Anal. ($C_{21}H_{23}N_2OCl\cdot0.1H_2O$) C, H, N.

(7-Chloro-1,2,3,4-tetrahydro-1*H*-1-benzazepin-1-yl)-2-chloro-4-(pyrrolidin-1-yl)benzamide (23d). Using the same procedure as **23a, 23d** (0.78 g, 83%) was obtained as a white powder from **11** (0.44 g, 2.4 mmol) and **22b** (0.55 g, 2.4 mmol): mp 137−138 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32−2.28 (8H, m), 2.49−3.77 (7.16H, m), 4.78−5.10 (0.84H, m), 6.12 (0.84H, dd, J = 8.5, 2.2 Hz), 6.37 (0.84H, d, J = 2.2 Hz), 6.42−6.59 (0.32H, m), 6.72 (0.84H, d, J = 8.5 Hz), 6.81 (0.84H, d, J = 8.4 Hz), 6.89 (0.84H, dd, J = 8.4, 2.3 Hz), 7.12 (0.84H, d, J = 2.3 Hz), 7.17−7.39 (0.64H, m). Anal. ($C_{21}H_{22}N_2OCl_2$) C, H, N.

(1,2,3,4-Tetrahydro-1*H*-1-benzazepin-1-yl)-2-chloro-4-(piperidin-1-yl)benzamide (23e). Using the same procedure as **23a, 23e** (0.42 g, 40%) was obtained as a white powder from **12** (0.42 g, 2.8 mmol) and **22e** (0.5 g, 1.8 mmol): mp 150−152 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.34−2.18 (10H, m), 2.57−3.86 (7.2H, m), 4.83−5.03 (0.8H, m), 6.47 (0.8H, dd, J = 8.6, 2.4 Hz), 6.65−7.44 (6.2H, m). Anal. ($C_{22}H_{25}N_2OCl$) C, H, N.

(1,2,3,4-Tetrahydro-1*H*-1-benzazepin-1-yl)-4-(morpholin-1-yl)benzamide (23f). Using the same procedure as **23a, 23f** (0.45 g, 69%) was obtained as a white powder from **12** (0.26 g, 1.7 mmol) and **22f** (0.74 g, 3.1 mmol): mp 124−126 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31−2.21 (4H, m), 2.61−4.40 (11.2H, m), 4.80−5.09 (0.8H, m), 6.46 (0.8H, dd, J = 8.5, 2.1 Hz), 6.63−7.46 (6.2H, m). Anal. ($C_{21}H_{23}N_2O_2Cl$) C, H, N.

(1,2,3,4-Tetrahydro-1*H*-1-benzazepin-1-yl)-2-chloro-4-(pyrazol-1-yl)benzamide (23g). Using the same procedure as **23a, 23g** (0.48 g, 51%) was obtained as a white powder from **12** (0.4 g, 2.7 mmol) and **22g** (0.6 g, 2.7 mmol): mp 156−157 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.30−2.23 (4H, m), 2.68−3.75 (3.1H, m), 4.85−5.03 (0.9H, m), 6.37−6.55 (1H, m), 6.83−8.00 (8.1H, m). Anal. ($C_{20}H_{18}N_3OCl$) C, H, N.

(1,2,3,4-Tetrahydro-1*H*-1-benzazepin-1-yl)-2-chloro-4-(3-methylpyrazol-1-yl)benzamide (23h). Using the same procedure as **23a, 23h** (0.56 g, 60%) was obtained as a white powder from **12** (0.37 g, 2.5 mmol) and **22h** (0.6 g, 2.5 mmol): mp 117−120 °C; ^{1}H NMR (200 MHz, CDCl3) d 1.18−2.48 (7H, m), 2.67−3.82 (3.1H, m), 4.83−5.00 (0.9H, m), 6.15−6.32 (1H, m), 6.80−7.86 (8H, m). Anal. ($C_{21}H_{20}N_3OCl\cdot0.1H_2O$) C, H, N.

(1,2,3,4-Tetrahydro-1*H*-1-benzazepin-1-yl)-2-chloro-4-(3-methylpyrrolidin-1-yl)benzamide (23i). Using the same

procedure as **23a, 23i** (0.25 g, 32%) was obtained as a white powder from **12** (0.3 g, 2.1 mmol) and **22i** (0.5 g, 2.1 mmol): mp 130.5−131.5 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.07, 1.15 (total 3H, each d, J = 6.6 Hz), 1.31−2.52 (8H, m), 2.57−3.68 (8.1H, m), 4.83−5.14 (0.9 H, m), 6.05 (0.9H, dd, J = 8.5, 2.3 Hz), 6.26−6.58 (1.3H, m), 6.71 (0.9H, d, J = 8.5 Hz), 6.80−7.46 (3.9H, m). Anal. ($C_{22}H_{25}N_2OCl$) C, H, N.

Radioligand Binding Assay to HeLa Cells Expressing Human AVP Receptors. The procedures for the radioligand binding assay and the preparation of HeLa cells expressing the human V_2 receptor have been reported in detail.[8a,14] The experiments were performed after each cell reached confluence in 24-well dishes. After washing three times with ice-cold phosphate-buffered saline (PBS), the cells were incubated with [^{3}H]AVP with or without unlabeled AVP (final concentration of 1 μM) to determine the total binding or the nonspecific binding, respectively, in DMEM containing 0.3% BSA brought to a pH of 7.4 with 10 mM HEPES−NaOH. For the competition experiments, the test compounds dissolved in dimethyl sulfoxide (DMSO) and AVP dissolved in saline were diluted with the DMEM medium and added to each well at several appropriate concentrations. After incubation at 4 °C for 2 h, the reaction was stopped by removing the buffer, and the cells were rinsed three times with ice-cold PBS. The cells were lysed with 250 μL of 0.1 N NaOH containing 0.1% sodium dodecyl sulfate (SDS), transferred into scintillation vials, and mixed with 5 mL of Aquazol II (Packard, Tokyo, Japan). Radioactivity was detected using a liquid scintillation counter (LSC-1050; Aloka, Tokyo, Japan). The cells in some wells were lysed in 0.1 N NaOH and then protein contents were determined by the dye method (Bradford, 1976). IC_{50} values are the concentrations of compounds which inhibit [^{3}H]AVP binding by 50%. All assays were performed in duplicate. The intraassay and interassay IC_{50} values for the given compounds varied by less than 3% and less than 20%, respectively.

Cyclic AMP Production in HeLa Cells Expressing V_2 Receptors. After reaching confluence in 24-well dishes, the cells were washed twice with ice-cold PBS, incubated with the DMEM containing 0.3% BSA and 1 mM IBMX, and brought to a pH of 7.4 with 10 mM HEPES−NaOH. After the addition of certain concentrations of test compounds or AVP, the incubation was carried out at 37 °C for 10 min. The reaction was stopped by aspiration of the medium then the cells were rinsed twice with ice-cold PBS. Cyclic AMP was extracted from the cells by adding 250 μL of 0.1 N HCl and stored at −20 °C until the cAMP determination using a radioimmunoassay kit (Yamasa, Tokyo, Japan). All assays were performed in triplicate.

Data Analysis. The percentage of maximal cAMP accumulation (PMA) of each compound at 10^{-6} M was determined as the percent to the response with AVP (10^{-9} M). It was calculated using the equation: PMA (%) = ($cAMP_A$ − $cAMP_B$) × 100/($cAMP_V$ − $cAMP_B$), where $cAMP_A$ is the cAMP count using a compound at the given concentration, $cAMP_B$ is the cAMP count without a compound, and $cAMP_V$ is the cAMP count using AVP (10^{-9} M).

Conformational Energy Calculations. All calculations were performed using the CHARMM force field. Conformational searches were performed using QUANTA97 (MSI, 9685 Scranton Rd., San Diego, CA 92121-3752) to obtain stable conformers. Powell minimization with a maximum of 5000 iterations was used in the conformational search with the default convergence set at a value of 0.001 (kJ/mol)/Å. All superimpositions and calculations of solvent-accessible surface areas were performed using QUANTA97 with default parameters.

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Supporting Information Available: Tables 1 and 2 containing elemental analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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