Orally Active, Nonpeptide Vasopressin V₂ Receptor Antagonists: A Novel Series of 1-[4-(Benzoylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-benzazepines and Related Compounds

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This paper describes a novel series of nonpeptide vasopressin V₂ receptor antagonists. It has been demonstrated that the 1-[4-(benzoylamino)benzoyl]-2,3,4,5-1*H*-benzazepines and 1-[4-(benzoylamino)benzoyl]-2,3,4,5-1*H*-1,5-benzodiazepines show a high affinity for V₂ (and V₁ₐ) receptors. Among the 1-[4-(benzoylamino)benzoyl]-2,3,4,5-1*H*-benzazepine series, compounds with an alkylamino group on the benzazepine ring have been shown to have oral activity. A lipophilic group at the ortho position on the terminal benzoyl ring is important for both high V₂ receptor affinity and oral activity. On the basis of these favorable properties, clinical testing of **31b** has begun for use as an oral and iv aquaretic agent.

The neurohypophysial nonapeptide hormone arginine vasopressin (AVP) is well known for its pressor response and antidiuretic activities in mammals. AVP exerts vasoconstriction by interacting with the vascular V₁ₐ receptors and antidiuresis by interacting with the renal V₂ receptors.[1−3] These mechanisms help to maintain normal plasma osmolality, blood volume, and blood pressure. AVP antagonists would be expected to be novel therapeutic agents for the treatment of diseases characterized by the excessive renal reabsorption of free water.[4] Until recently, all potent AVP receptor antagonists reported have been peptide analogues of AVP[1−4] and have had poor oral bioavailability, with some exhibiting partial agonistic activity.[6,7] Recently, we[8] and others[9] reported orally effective nonpeptide AVP V₁ₐ antagonists.

In this paper, we describe the brief history of the development of our orally effective, nonpeptide AVP V₂ receptor antagonists. We previously reported a series of 4-(substituted benzoyl)piperidyl 2,3-dihydro quinolinones to be orally effective AVP V₁ₐ receptor antagonists.[8] Although none of the previously reported analogues exhibited any apparent V₂ binding affinity, we have conducted further investigations to find a V₂ antagonist. Starting from the structure of **1**, which shows an affinity of 78 µM for V₂ binding, we synthesized a series of more rigid analogues by replacing the piperidyl moiety of **1** with a phenyl ring. In our study of the V₁ₐ antagonist series we found that the two amide moieties in compound **1** were essential for the affinity to AVP receptors. Furthermore, we were interested in reversing the amide linkage in the 3,4-dihydro-2(1*H*)-quinolinone skeleton of compound **1** and achieving a normal peptide bond arrangement (*CON* ⟳ *NCO* → *NCO* ⟳ *NCO*). The resultant structure is shown in **2**.

Those studies led to the discovery of 1-benzoylbenzazepines as potent, orally bioavailable V₂ receptor antagonists. These compounds are exemplified by **31b**, which is now undergoing clinical evaluation as a cardiovascular drug.

1 IC₅₀ (µM) V₁ = 1.2, V₂ = 78   **2**
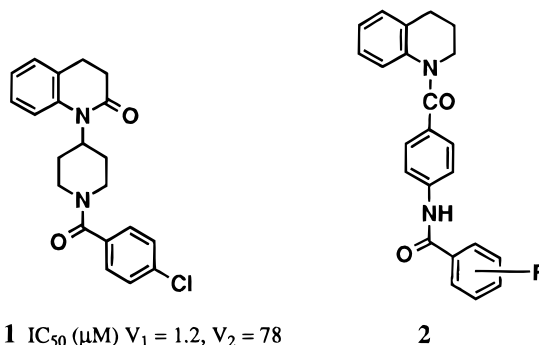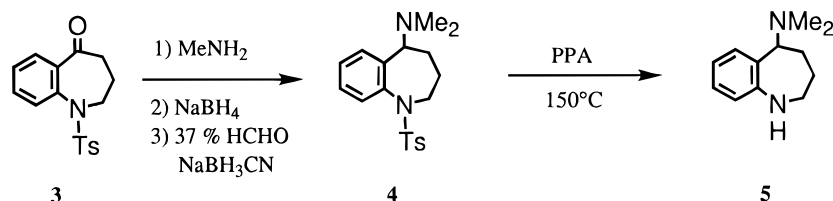
Chemistry

The synthetic pathway for the preparation of almost all compounds listed in Tables 1−6 is shown in Schemes 1 and 2. The benzazepin-5-one **3**[10] was converted to the dimethylamino compound **4** in three steps by twice using reductive amination (reaction with methylamine and sodium borohydride, followed by treatment with formaldehyde and sodium cyanoborohydride). Deprotection of the tosyl group of **4** was accomplished by heating in polyphosphoric acid to produce **5**. This reaction could not be completed when concentrated hydrochloric acid was used in acetic acid at reflux temperature within 7 h.

Benzene-fused hetero rings (**5**−**15**) were converted into aniline intermediates **17** by the simple transformations shown in Scheme 2. The starting materials were commercially available or were prepared by published procedures.[11−19] The amides of Table 1−5 were obtained by acylation of the anilines with a wide variety of acid chlorides. The complicated NMR spectra of this series is due to the presence of a rotational barrier, and measurements at an elevated temperature (120 °C) of **31b** showed a simplified spectrum (see the Experimental Section). The urethane **29a**, the sulfonamide **29b**, and the urea **29c** were prepared by combining the aniline **17f** with chloroformate, sulfonyl chloride, or isocyanate, respectively.
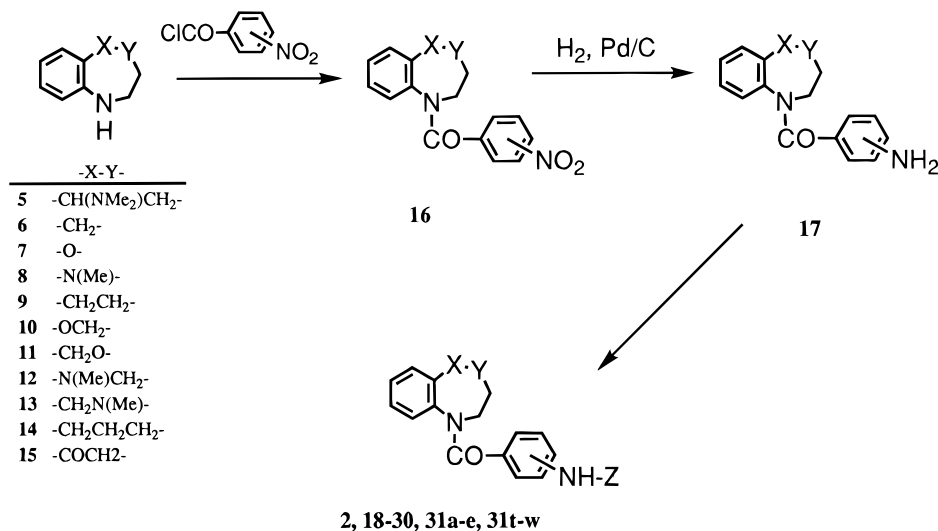
Modifications at the 5-position of the benzazepines are shown in Schemes 3 and 4. The monoalkylamines

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Scheme 1

Scheme 2

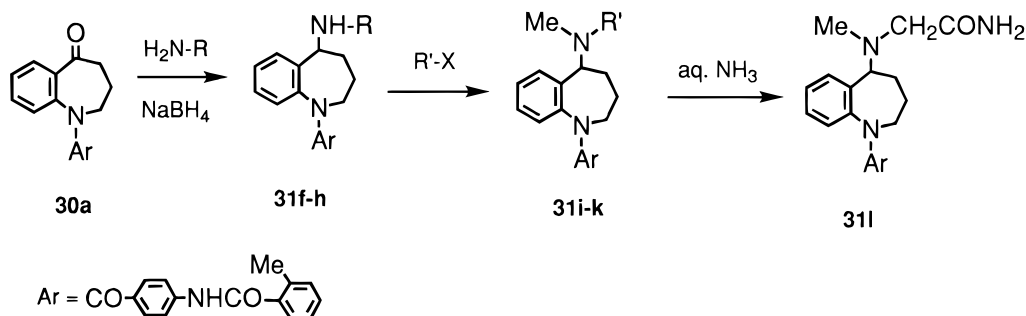|	-X-Y-
5	-CH(NMe$_2$)CH$_2$-
6	-CH$_2$-
7	-O-
8	-N(Me)-
9	-CH$_2$CH$_2$-
10	-OCH$_2$-
11	-CH$_2$O-
12	-N(Me)CH$_2$-
13	-CH$_2$N(Me)-
14	-CH$_2$CH$_2$CH$_2$-
15	-COCH2-

2, 18-30, 31a-e, 31t-w

Scheme 3

31f−h were prepared from the ketone **30a** with alkyl-amines by reductive amination. Compound **31f** was reacted with alkyl halides in the presence of anhydrous potassium carbonate to give alkyl-substituted methyl-amino compounds **31i,j**. Condensation of **31f** and gly-colonitrile provided the acetonitrile **31k**. Treatment of compound **31j** with methanolic ammonia afforded the amide **31l**.

Alternatively, simple amino compound **31n** was pre-pared for comparison purposes with derivatives of the monoalkylamines **31f−h**, as shown in Scheme 4. Con-densation of the ketone **30a** with hydroxylamine af-forded oxime intermediate, which was converted into the acetoxime **31m** by the reaction with acetic anhy-dride. Reduction of **31m** by catalytic hydrogenation (PtO$_2$) gave the amino compound **31n**. The acetamide **31q** and the urea **31r** were prepared from the amine **31n** by the reaction with acetic anhydride and methyl isocyanate, respectively. The reaction of the ketone **30a** with sodium borohydride gave the alcohol **31p**. The piperidine **31o** was prepared by the reaction of **30b** and piperidine in the presence of titanium chloride as a Lewis acid catalyst, followed by the reduction with sodium borohydride in methanol. Reduction of the

corresponding nitro **31w** gave **31x**. The amine **31x** was acylated with acetic anhydride to afford the amide **31y**.

N-Methylation of amide nitrogen in compound **31b** was carried out using sodium hydride/DMF and the methyl iodide to produce **31s**.

Biological Methods

The method for determination of AVP (rat liver = V$_{1a}$ and rat kidney = V$_2$) receptor binding have been published elsewhere.[20−23] Assays for antidiuretic V$_2$ antagonism were performed as described separately.[22] Briefly, these examinations were performed by measur-ing changes in urine flow in hydrated conscious rats. After oral administration of the compounds, spontane-ously voided urine was collected every 2 h for an 8 h period. The dose of the compound needed to produce a 3-fold increase in urine volume for 2 h as compared to that of control rats was used as the ED$_3$ value to estimate the potency of the compound.

Results and Discussion

The compounds were tested primarily with respect to their affinity for AVP receptors as measured by their
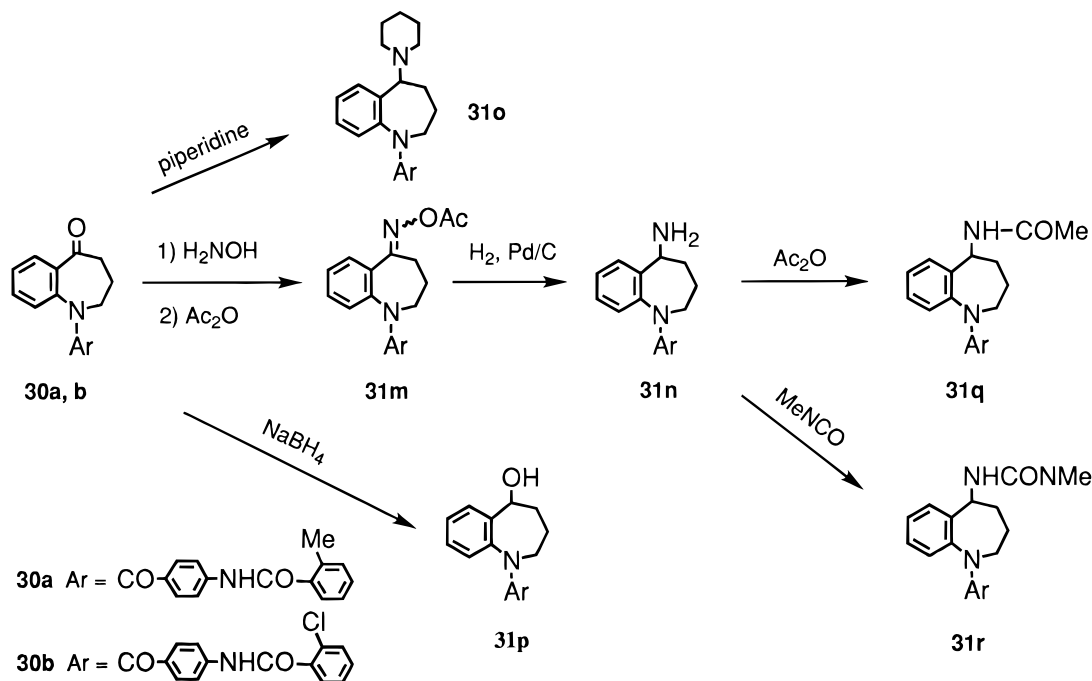
Scheme 4

30a Ar = CO–⟨phenyl⟩–NHCO–⟨2-Me-phenyl⟩

30b Ar = CO–⟨phenyl⟩–NHCO–⟨2-Cl-phenyl⟩

Table 1. Binding Affinities of 1,2,3,4-Tetrahydroquinoline Derivatives

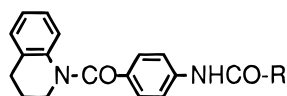| no.	subst pos	R	mp (°C)	formula[a]	IC$_{50}$[b] (μM) V$_{1a}$	V$_2$
2a	4	4-Cl	200.5−201.5	C$_{23}$H$_{19}$ClN$_2$O$_2$	5.1	1.9
2b	4	4-OMe	176−177	C$_{24}$H$_{22}$N$_2$O$_3$	2.2	1.8
2c	4	4-OEt	219−220	C$_{25}$H$_{24}$N$_2$O$_3$·$^1/_2$H$_2$O	14	>100
2d	4	4-OBu	193−194	C$_{27}$H$_{28}$N$_2$O$_3$	>100	>100
2e	4	4-Me	202−203	C$_{24}$H$_{22}$N$_2$O$_2$	10	1.4
2f	4	4-NO$_2$	263.5−264.5	C$_{23}$H$_{19}$N$_3$O$_4$	>100	6.5
2g	4	H	202.5−203.5	C$_{23}$H$_{20}$N$_2$O$_2$·$^1/_4$H$_2$O	1.6	0.98
2h	4	2-Cl	225−226	C$_{23}$H$_{19}$ClN$_2$O$_2$	1.6	0.42
2i	4	2-OMe	175.5−176.5	C$_{24}$H$_{22}$N$_2$O$_3$·$^1/_4$H$_2$O	1.9	2.1
2j	4	2-Me	224−225	C$_{24}$H$_{22}$N$_2$O$_2$	1.4	0.20
2k	4	2-NO$_2$	231−232	C$_{23}$H$_{19}$N$_3$O$_4$	2.7	0.53
2l	4	3-Cl	210−211	C$_{23}$H$_{19}$ClN$_2$O$_2$	6.4	0.20
2m	4	3-OMe	143−144	C$_{24}$H$_{22}$N$_2$O$_3$	2.8	0.40
2n	4	3-Me	178−179	C$_{24}$H$_{22}$N$_2$O$_2$	3.1	0.68
2o	4	3-NO$_2$	178.5−179.5	C$_{23}$H$_{19}$N$_3$O$_4$	16	0.76
2p	4	3,4-Me$_2$	182.5−183.5	C$_{25}$H$_{24}$N$_2$O$_2$·$^1/_4$H$_2$O	>100	1.2
2q	4	2,4-Me$_2$	189−190	C$_{25}$H$_{24}$N$_2$O$_2$	3.3	0.21
2r	4	2,4-Cl$_2$	183−184	C$_{23}$H$_{18}$N$_2$O$_2$Cl$_2$	>100	0.25
2s	4	3,5-Cl2	231−232	C$_{23}$H$_{18}$N$_2$O$_2$Cl$_2$	9.4	0.082
18	3	H	c	C$_{23}$H$_{20}$N$_2$O$_2$·$^1/_4$H$_2$O	>100	40
19	2	H	126−127	C$_{23}$H$_{20}$N$_2$O$_2$	88	22

[a] Analysis for C, H, and N were within ±0.4% of theory. [b] Compounds were tested for their ability to displace [³H]AVP from its specific binding sites in rat liver (V$_{1a}$ receptor) and kidney (V$_2$ receptor) plasma membrane preparations (see the Experimental Section). [c] Amorphous solid.

ability to displace [³H]AVP from its specific binding sites in rat liver (V$_{1a}$ receptor) and kidney (V$_2$ receptor) plasma membranes, respectively; the data are reported in Tables 1−5 as IC$_{50}$ values.

Replacement of the piperidine ring of compound **1** by a phenyl ring resulted in a benzamide **2a**, which greatly enhanced V$_2$ binding affinity. The success of compound **2a** prompted us to search for a V$_2$ receptor antagonist. The longer alkoxy chain was introduced on the terminal phenyl ring as seen with compounds **2b−d**, with 4-OEt being the optimal substituent for the V$_{1a}$ antagonist

series. However, the introduction of a longer alkoxy chain, as in compounds **2c** and **2d**, drastically lowered not only V$_2$ binding affinity but also V$_{1a}$ binding affinity. The interaction of compound **2a** with the AVP receptor seems to be different from that of the 2(1*H*)-quinolinones in the V$_{1a}$ antagonist series.

Comparison of **2g**, **18**, and **19** showed that the substituted position of benzamide must be para to the tetrahydroquinolinylcarbonyl group for the greatest binding affinity to both V$_{1a}$ and V$_2$ receptors, while ortho (**19**) followed by meta (**18**) substitution decreases the

Table 2. AVP V_{1a}, V_2 Receptor Binding Affinities for 1-(4-Amidobenzoyl)-1,2,3,4-tetrahydroquinolines

				IC$_{50}$[b] (μM)	
no.	R	mp (°C)	formula[a]	V_{1a}	V_2
20a	Me	c	$C_{18}H_{18}N_2O_2 \cdot H_2O$	74	>100
20b	Pr	134–135	$C_{20}H_{22}N_2O_2$	4.3	7.1
20c	i-Pr	182.5–183.5	$C_{20}H_{22}N_2O_2$	2.4	8.1
20d	CH$_2$Ph	c	$C_{24}H_{22}N_2O_2 \cdot \frac{1}{4}H_2O$	3.2	1.0
20e	CH$_2$CH$_2$Ph	155–156	$C_{25}H_{24}N_2O_2$	2.3	6.1
20f	3-pyridyl	212.5–213.5	$C_{22}H_{19}N_3O_2$	11	7.6
20g	2-furanyl	193–194	$C_{21}H_{18}N_2O_3 \cdot \frac{1}{4}H_2O$	4.0	6.4
20h	3-thienyl	203–204	$C_{21}H_{18}N_2O_2S$	1.7	1.7

$^{a-c}$ See Table 1 for an explanation of tabulated data.

affinity. The substitution on the terminal phenyl ring showed that the ortho and meta positions were always superior to the para position in V_2 affinity (**2a,b,e–o**), except for the 2-OMe group (**2i**). Thus, compounds **2a,b,e,f** have lower V_2 binding affinities than the unsubstituted benzamide **2g** due to increased steric interactions between this region of the terminal aromatic ring and the receptor site. Substituents on the meta and ortho (**2h,j–o**) positions show a slight enhancement of V_2 binding affinity. The most potent compound in the series was the 3,5-Cl$_2$ (**2s**), a significant 22-fold improvement over the 4-Cl lead **2a**. Surprisingly, the 2,4-disubstitution on the phenyl ring led to a retention of V_2 binding (**2q,r** vs **2a,e** and **2h,j**). It is unclear why **2q,r** does not show lower V_2 binding affinity than the ortho- or meta-monosubstitution (**2h,j**). The presence of ortho substituents on the phenyl ring might force a conformational change, consequently reducing the interactions between para-substitution and the receptor site.

More substantive changes in the benzamide are shown in Table 2. The alkyl group (**20a–c**) produced a substantial decrease in V_2 affinity. Insertion of a methylene spacer between the carbonyl and phenyl ring proved compatible with V_2 affinity (**20d** vs **2g**); however, the addition of a longer chain, as in **20e**, reduced potency. Other replacements for the phenyl ring, such as pyridyl (**20f**), furyl (**20g**), and thienyl (**20h**), proved less effective.

On the basis of these studies, the 2-methylbenzamide **2j** was selected for further investigation. Replacements of the tetrahydroquinoline ring of the new lead **2j** with other benzene-fused heterocycles are shown in Table 3. In the six-membered ring series, the insertion of a hetero atom to the tetrahydroquinoline ring decrease V_2 binding affinity, as seen with compounds **21** and **22**. However, the enlargement of six-membered rings to seven-membered rings have a striking effect on V_2 binding affinity (**21** vs **24**, **22** vs **26**, and **2j** vs **23a**). Remarkably, compounds **23a** and **23b** bound to the V_2 receptor with an affinity approximately 1 order of magnitude higher than **2j** and **2h**, respectively. Moreover, **23a,b** increased V_{1a} binding by 2 orders of magnitude over **2j,h**. Increased steric bulkiness and/or lipophilicity of seven-membered rings compared to that of between 2- and 3-position of six-membered rings might be responsible for enhanced binding affinity. Interestingly, compound **26** shows V_2 selective binding affinity. The benzazocine **28**, 5-methyl-1,5-benzodiaz-

epine **26**, and benzazepine **23a** all have very similar V_2 binding affinity.

Compounds **29a–c** in Table 4 were prepared to check the necessity for the amide linkage of the benzamide substructure in compound **23a**. Replacement with the urethane **19a**, sulfonamide **29b**, or urea **29c** caused a substantial drop in V_2 receptor affinity when compared with **23c**.

The potent V_2 binders **23a,b**, and **28** in Table 3 failed to demonstrate oral diuretic activity. However, the 1,4-benzodiazepine **27**, which showed lower V_2 affinity, did provide some oral diuretic activity, with a 5- to 6-fold increase in urine volume being observed for 4 h at 100 mg/kg in normally hydrated conscious rats ($n = 3$) over the control rats ($n = 6$). This may have been due to a greater oral bioavailability of 1,4-benzodiazepine. In an attempt to produce an analogue having greater potency, bioavailability, and V_2 selective binding affinity, we decided to investigate the effect of introducing a basic functional group, such as a dimethylamine, into the benzazepine ring of compounds **23a,b**, which have potent V_{1a} and V_2 binding affinity. In consideration of synthetic simplicity, the 5-position of benzazepine was selected for the introduction of an amino group.
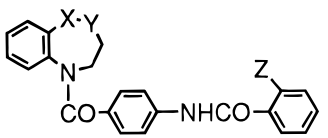
The 5-dimethylaminobenzazepines **31a–e** led to a retention of potent V_2 binding affinity and a reduction of the V_{1a} binding affinity (Table 5). The effect of the substitution pattern in the terminal phenyl ring followed the same trends as those seen earlier. Thus, the placement of 2-Me (**31b**) and 3-Me (**31c**) increased V_2 binding affinity over the nonsubstituted congener (**31a**), while the para substituent (**31d**) was slightly detrimental to V_2 binding. A comparison of V_2 binding affinity within a class of compounds (**31b,f–l,n**) indicates that this series of V_2 receptor antagonists, with the exception of the cyclic analog **31o**, is relatively insensitive to the nature of an alkyl substituent on the amino group of the benzazepine ring. The replacement acetamide **31q** and the urea **31r** demonstrated poor affinity for V_2 receptor when compared with the amine **31n** or monoalkylamino series **31f–h**. This loss of affinity is not believed to be due to the absence of a basicity of amines, since the hydroxy **31p** shows potent V_2 binding affinity.

The introduction of a 3,5-Cl$_2$ substituent on the terminal phenyl ring, which showed the highest binding affinity in the tetrahydroquinoline series, was about as potent as 2,4-Cl$_2$ or 2-Cl (**31t** vs **31u** and **31e**).

N-Methylation of the amide nitrogen, as in compound **31s** drastically lowered the V_2 binding affinity by 2 orders of magnitude when compared with compound **31b**. It seems that either the tertiary amide arranges an unfavored conformation for binding or it is necessary to have a hydrogen bonding interaction between the amide moiety and the receptor.[24]
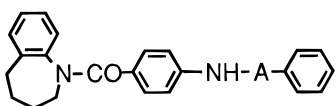
More importantly, some of these analogues show oral activity. In the dimethylamino series **31a–e**, the 2-Me (**31b**) demonstrated potent oral activity in rats, whereas H (**31a**) and 3-Me (**31c**) showed no activity. In a simple alkylamino series **31b** and **31e–i**, the relative orders of potency of the in vitro assay translate into in vivo diuretic activity. However, additional substitution on the alkyl group, as seen with compounds **31j–l**, are detrimental to oral activity.

Compounds **31v–y** were prepared for comparison

Table 3. AVP V$_{1a}$, V$_2$ Receptor Binding Affinities for Benzene-Fused Heterocycles

no.	−X−Y−	Z	mp (°C)	formula[a]	IC$_{50}$[b] (μM) V$_{1a}$	V$_2$
21	−O−	Me	213−214	C$_{23}$H$_{20}$N$_2$O$_3$	7.7	4.1
22	−N(Me)−	Me	207−208	C$_{24}$H$_{22}$N$_2$O$_3$·$\frac{1}{4}$H$_2$O	5.1	0.40
23a	−CH$_2$CH$_2$−	Me	225.5−226.5	C$_{25}$H$_{24}$N$_2$O$_2$	0.056	0.018
23b	−CH$_2$CH$_2$−	Cl	211.5−212.5	C$_{24}$H$_{21}$ClN$_2$O$_2$	0.045	0.029
23c	−CH$_2$CH$_2$−	H	230.5−231.5	C$_{24}$H$_{22}$N$_2$O$_2$·$\frac{1}{8}$H$_2$O	0.095	0.070
24	−OCH$_2$−	Me	219−220	C$_{24}$H$_{22}$N$_2$O$_3$·$\frac{1}{4}$H$_2$O	1.2	0.11
25	−CH$_2$O−	Me	202−203	C$_{24}$H$_{22}$N$_2$O$_3$	0.63	0.30
26	−N(Me)CH$_2$−	Me	222.5−223.5	C$_{25}$H$_{25}$N$_3$O$_2$	0.38	0.014
27	−CH$_2$N(Me)−	Me	276−281	C$_{25}$H$_{25}$N$_3$O$_2$·HCl	1.8	0.17
28	−CH$_2$CH$_2$CH$_2$−	Me	198−199	C$_{26}$H$_{26}$N$_2$O$_2$	0.41	0.028

[a,b] See Table 1 for an explanation of tabulated data.

Table 4. Effects of Amido Surrogates

no.	−A−	mp (°C)	formula[a]	IC$_{50}$[b] (μM) V$_{1a}$	V$_2$
29a	−COO−	199−201	C$_{24}$H$_{22}$N$_2$O$_3$	7.8	0.79
29b	−SO$_2$−	178−182.5	C$_{23}$H$_{22}$N$_2$O$_3$S	2.5	1.6
29c	−CONH−	244−245	C$_{24}$H$_{23}$N$_3$O$_2$	0.76	0.18

[a,b] See Table 1 for an explanation of tabulated data.

with 2-Me (**31b**). The replacement of the methyl with OMe (**31v**) or NO$_2$ (**31w**) lowered V$_2$ binding affinity, as was seen previously in the tetrahydroquinoline series. The amine **31x** and the acetamide **31y** showed much less activity than **31b**. Lipophilic groups at this site seemed to provide better V$_2$ receptor ligands.

The results of in vitro and in vivo examinations of **31b** (OPC-31260) are presented in detail in separate reports.[22] These studies indicated that the compound is an effective, orally bioavailable vasopressin V$_2$ receptor antagonist. In alcohol-anesthetized rats, **31b** effectively blocked AVP-induced antidiuretic action with no agonistic properties. In normal conscious rats, it increased urine flow and decreased urine osmolality by oral administration (1−30 mg/kg). Thus, **31b** is a selective V$_2$ receptor antagonist which acts as an aquaretic agent. It is currently undergoing human trials as a hydrochloride salt.[25,26]

In conclusion, in this report we described the development of the 1-benzoylbenzazepine OPC-31260 (**31b**). This compound is the first reported example of a nonpeptide antagonist for vasopressin V$_2$ receptors, and it demonstrates oral activity. Moreover, **31b** has achieved the important goal of an aquaretic effect in humans, as reported elsewhere.[25,26] Such properties are absent in currently available peptide compounds.

Although the goal of the present study was to search for an orally effective V$_2$ selective vasopressin antagonist, we also described herein compounds which shows high affinity for both V$_{1a}$ and V$_2$ receptors.

From the study of structure−activity relationships, we discovered that the benzene-fused seven-membered ring system, as shown in Table 3 is excellent for V$_2$ (and V$_{1a}$) antagonists. The introduction of an alkylamino group at the 5-position of the benzazepine ring give rise to oral activity. Comparison among the potent analogues **31b,f−l,n,p** indicates that a variety of substituents are tolerated on the azepine ring. This suggests that the AVP receptor is quite permissive in accepting this region of the nonpeptide antagonist. The ortho substituents on the terminal benzoyl ring seem to be important both for a high affinity for the V$_2$ receptors and for good oral activity, while the meta substituents possess good V$_2$ affinity, but have decreased oral activity.
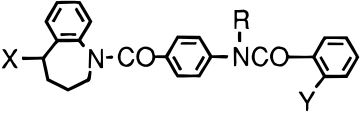
We believe that the compounds described in this paper, in particular OPC-31260, will be useful for the treatment of cardiovascular diseases.

Experimental Section

Melting points were determined by a Yanagimoto Micro Point Apparatus and were uncorrected. ^{1}H-NMR spectra were recorded on either a Bruker AC-200 (200 MHz) spectrometer or a Bruker AC-250 (250 MHz) spectrometer using tetramethylsilane (TMS) or 3-(trimethylsilyl)propionic acid-d_5 (TSP) as an internal standard. Elemental analyses were determined with on a Yanaco MT-5 CHN CORDER and were within ±0.4% of theory unless noted otherwise. All compounds were routinely checked by TLC with Merck silica gel 60 F254 precoated plates.

5-(Dimethylamino)-2,3,4,5-tetrahydro-1*H*-benzazepine (4). Tosylbenzazepinone **3** (0.60 g, 1.9 mmol), 40% methylamine methanol solution (6 mL), molecular sieves (4A, 1.2 g), and methanol (6 mL) were mixed and refluxed for 5 h. After cooling to room temperature, dichloromethane (10 mL) was added to the mixture, and the mixture was filtered through Celite and concentrated. The residue was dissolved in methanol (30 mL), and NaBH$_4$ (0.10 g, 2.7 mmol) was added to the solution at 0−4 °C. The mixture was stirred for 1 h at room temperature and concentrated. The residue was poured into water and extracted with dichloromethane. The organic layers were dried over magnesium sulfate and concentrated to give 5-(methylamino)-1-tosyl-2,3,4,5-tetrahydro-1*H*-benzazepine (0.54 g) as a pale brown oil: NMR (CDCl$_3$) δ 1.2−2.1 (m, 5H), 2.16 (s, 3H), 2.42 (s, 3H), 3.0−4.3 (m, 3H), 7.1−7.5 (m, 6H), 7.67 (d, J = 8.0 Hz, 2H).

To a mixture of the above methylamine (0.54 g), methanol (6 mL), 37% HCHO (0.70 mL, 8.6 mmol), and NaBH$_3$CN (0.15 g, 2.4 mmol) was added acetic acid (0.4 mL, 6.7 mmol) at 0−4 °C. The mixture was stirred for 1 h at room temperature and concentrated. The residue was poured into water and basified with 10% aqueous potassium carbonate solution, and extracted with dichloromethane. The organic layers were washed with water, dried over magnesium sulfate, and concentrated to give **4** (0.51 g, 78%) as pale brown oil which was employed in the

Table 5. Effects of 5-Position Substituents on the Benzazepine Ring

no.	X	R	Y	mp (°C)	formula[a]	IC$_{50}$[b] (μM) in vivo		
						V$_{1a}$	V$_2$	UV[c] (ml)
31a	NMe$_2$	H	H	221–223	C$_{26}$H$_{27}$N$_3$O$_2$	3.0	0.027	(>30)[d]
31b	NMe$_2$	H	2-Me	207–208	C$_{27}$H$_{29}$N$_3$O$_2$	1.4	0.012	12.3 ± 2.3 (ED$_3$ = 3.8)
31c	NMe$_2$	H	3-Me	171–173	C$_{27}$H$_{29}$N$_3$O$_2$	2.4	0.014	(>30)
31d	NMe$_2$	H	4-Me	185–187	C$_{27}$H$_{29}$N$_3$O$_2$	26	0.044	
31e	NMe$_2$	H	2-Cl	213–214	C$_{26}$H$_{26}$ClN$_3$O$_2$	3.0	0.027	7.0 ± 0.5 (4.2)
31f	NHMe	H	2-Me	210–211	C$_{26}$H$_{27}$N$_3$O$_2$·$^1\!/_4$H$_2$O	0.72	0.024	8.3 ± 2.5 (4.6)
31g	NHEt	H	2-Me	135.5–137	C$_{27}$H$_{29}$N$_3$O$_2$·H$_2$O[e]	1.6	0.029	5.4 ± 0.6 (8.0)
31h	NHPr	H	2-Me	170–171	C$_{28}$H$_{31}$N$_3$O$_2$·$^1\!/_4$H$_2$O[f]	0.89	0.050	5.6 ± 1.0 (6.6)
31i	N(Me)Pr	H	2-Me	163–163.5	C$_{29}$H$_{33}$N$_3$O$_2$	1.2	0.022	8.3 ± 1.8 (4.9)
31j	N(Me)CH$_2$CO$_2$Et	H	2-Me	167–168	C$_{30}$H$_{33}$N$_3$O$_4$	0.98	0.029	(>30)
31k	N(Me)CH$_2$CN	H	2-Me	227–228	C$_{28}$H$_{28}$N$_4$O$_2$	3.2	0.025	(>30)
31l	N(Me)CH$_2$CONH$_2$	H	2-Me	g	C$_{28}$H$_{30}$N$_4$O$_3$·$^1\!/_2$H$_2$O	0.29	0.013	6.2 ± 0.6 (6.4)
31m	=N∼OAc	H	2-Me	190–191	C$_{27}$H$_{25}$N$_3$O$_4$	2.3	0.058	(>30)
31n	NH$_2$	H	2-Me	198.5–199.5	C$_{25}$H$_{25}$N$_3$O$_2$	0.39	0.032	
31o	piperidyl	H	2-Cl	236–239	C$_{29}$H$_{30}$ClN$_3$O$_2$	2.8	0.14	
31p	OH	H	2-Me	197–199	C$_{25}$H$_{24}$N$_2$O$_3$	0.14	0.029	3.6 ± 0.8
31q	NHAc	H	2-Me	297–299	C$_{27}$H$_{27}$N$_3$O$_3$·EtOH	3.2	0.15	(>30)
31r	NHCONHMe	H	2-Me	286–287	C$_{27}$H$_{28}$N$_4$O$_3$·$^3\!/_4$H$_2$O[h]	2.8	0.096	
31s	NMe$_2$	Me	2-Me	182–182.5	C$_{28}$H$_{31}$N$_3$O$_2$·$^1\!/_4$H$_2$O	19	1.0	
31t	NMe$_2$	H	3,5-Cl$_2$	216–218	C$_{26}$H$_{25}$Cl$_2$N$_3$O$_2$	2.6	0.020	
31u	NMe$_2$	H	2,4-Cl$_2$	181–183	C$_{26}$H$_{25}$Cl$_2$N$_3$O$_2$	1.3	0.013	
31v	NMe$_2$	H	2-OMe	190–192	C$_{27}$H$_{29}$N$_3$O$_3$·$^1\!/_4$H$_2$O	1.0	0.077	
31w	NMe$_2$	H	2-NO$_2$	235–238	C$_{26}$H$_{26}$N$_4$O$_4$	2.6	0.071	
31x	NMe$_2$	H	2-NH$_2$	224–227	C$_{24}$H$_{28}$N$_4$O$_2$	1.9	0.19	
31y	NMe$_2$	H	2-NHAc	226–229	C$_{28}$H$_{30}$N$_4$O$_3$·$^1\!/_4$H$_2$O	16	0.64	

[a] Except where indicated, satisfactory analyses (±0.4%) were obtained for C, H, N. [b] See Table 1 for an explanation of tabulated data. [c] UV values mean 2-h urine volume (mL) when the test compounds were administered orally at a dose of 10 mg/kg and are expressed as a mean ± SEM (n = 4). The mean value of 2-h urine volume of control rats was 1.1 ± 0.2 mL (n = 4). [d] Values in parentheses indicate ED$_3$ value. ED$_3$ represents the dose (mg/kg) required for a 3-fold increase in the 2-h urine volume over the control rats. ED$_3$ values were obtained from a dose−response curve generated from three or four doses. Values such as >30 designate that at this dose (mg/kg) a 3-fold increase in the 2-h urine volume was not observed when compared with that of the control rats. [e] N: calcd, 9.43; found, 8.74. [f] N: calcd, 9.42; found, 9.01. [g] Amorphous solid. [h] N: calcd, 11.92; found, 12.41.

following reaction without further purification: NMR (CDCl$_3$) δ 1.31−1.82 (m, 4H), 2.02 (s, 6H), 2.41 (s, 3H) 2.76 (dd, J = 9.5, 3.5 Hz, 1H), 3.62 (br s, 2H), 7.14−7.53 (m, 6H), 7.66 (d, J = 8.2 Hz, 2H). A sample for elemental analysis was obtained as follows. A part of the crude **4** was treated with methanolic hydrogen chloride and concentrated. The residue was crystallized from ethanol to give **4·HCl** as colorless platelets: mp 210−211 °C. Anal. (C$_{19}$H$_{24}$N$_2$O$_2$S·HCl) C, H, N.

5-(Dimethylamino)-2,3,4,5-tetrahydro-1*H*-benzazepine (5). A mixture of **4** (7.0 g, 20 mmol) and polyphosphoric acid (80 g) was stirred at 150 °C for 2 h. The mixture was poured into ice−water and basified with 10% aqueous NaOH, and extracted with dichloromethane. The organic layers were dried over magnesium sulfate and concentrated to give **5** (3.8 g, 97%) as a brown oil: NMR (CDCl$_3$) δ 1.54−1.78 (m, 2H), 2.06−2.22 (m, 2H), 2.14 (s, 6H), 2.87 (ddd, J = 12.5, 10.8, 2.5 Hz, 1H), 3.07 (dd, J = 6.1, 1.5 Hz, 1H), 3.30−3.52 (m, 1H), 3.60 (br s, 1H), 6.70 (dd, J = 7.5, 1.2 Hz, 1H), 6.81 (dt, J = 7.5, 1.2 Hz, 1H), 7.05 (dt, J = 7.5, 1.6 Hz, 1H), 7.14 (dd, J = 7.5, 1.6 Hz, 1H). Anal. (C$_{12}$H$_{18}$N$_2$) C, H, N.
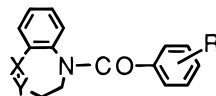
1-(4-Nitrobenzoyl)-1,2,3,4-tetrahydroquinoline (16a). To a solution of 1,2,3,4-tetrahydroquinoline **6** (25.0 g, 0.188 mol) and triethylamine (24.7 g) in dichloromethane (300 mL) was added portionwise *p*-nitrobenzoyl chloride (34.8 g, 0.188 mol) at 0−5 °C, and the mixture was stirred for 1 h at room temperature. The mixture was poured into water and extracted with dichloromethane. The organic layers were washed with water, dried over magnesium sulfate, and concentrated. The resulting residue was triturated with hexane to afford **16a** (35.3 g, 67%) as a yellow powder: mp 86−88 °C; NMR (CDCl$_3$) δ 2.09 (quint, J = 6.6 Hz, 2H), 2.87 (t, J = 6.5 Hz, 2H), 3.94 (t, J = 6.6 Hz, 2H), 6.3−6.7 (m, 1H), 6.86 (dd, J = 7.4, 7.4 Hz, 1H), 7.04 (dd, J = 7.4, 7.4 Hz, 1H), 7.21 (d, J = 7.3 Hz, 1H),

7.49 (d, J = 8.7 Hz, 1H), 8.12 (d, J = 8.7 Hz, 1H). Anal. (C$_{23}$H$_{28}$N$_2$O$_2$) C, H, N.

1-(4-Aminobenzoyl)-1,2,3,4-tetrahydroquinoline (17a). A mixture of **16a** (35.2 g, 0.125 mol), 10% palladium/carbon (3.0 g), and ethanol (400 mL) was stirred at room temperature under hydrogen atmosphere (1 atm) for 5 h. The mixture was filtered through Celite and evaporated. The residue was dissolved in dichloromethane, and this solution was washed with water, dried over magnesium sulfate, and concentrated. The resulting solid was washed with hexane to afford **17a** (31.5 g, 100%) as a yellow powder: mp 185−188 °C; NMR (CDCl$_3$) δ 2.03 (quint, J = 6.6 Hz, 2H), 2.82 (t, J = 6.6 Hz, 2H), 3.5−4.2 (m with s at δ 3.89 (J = 6.6 Hz), 4H), 6.4−6.6 (m, 2H), 6.65−6.8 (m, 1H), 6.88 (ddd, J = 7.3, 7.3, 1.7 Hz, 1H), 6.97 (ddd, J = 7.3, 7.3, 1.7 Hz, 1H), 7.05−7.4 (m, 3H). Anal. (C$_{23}$H$_{24}$N$_2$O$_4$) C, H, N.

1-[4-[(2-Methylbenzoyl)amino]benzoyl]-1,2,3,4-tetrahydroquinoline (2j). To a stirred solution of **17a** (0.50 g, 2.5 mmol) and triethylamine (0.3 g) in dichloromethane (20 mL) was added *o*-toluoyl chloride (0.40 g, 2.6 mmol) at 0−5 °C, and the mixture was stirred for 1 h at room temperature. The mixture was poured into water and extracted with dichloromethane. The organic layers were washed with water, dried over magnesium sulfate, and concentrated. Column chromatography (elution: 1−5% methanol/dichloromethane) provided **2j** (0.64 g, 86%) as a white solid: mp 153−155 °C; NMR (CDCl$_3$) δ 2.02 (quint, J = 6.6 Hz, 2H), 2.45 (s, 3H), 2.83 (t, J = 6.6 Hz, 2H), 3.83 (t, J = 6.6 Hz, 2H), 6.69 (d, J = 8.0 Hz, 1H), 6.8−7.7 (m, 11H), 8.03 (s, 1H). Anal. (C$_{23}$H$_{27}$N$_3$O$_2$) C, H, N.

1-[4-[(3-Thiophenecarbonyl)amino]benzoyl]-1,2,3,4-tetrahydroquinoline (20h). A mixture of 3-thiophenecarboxylic acid (0.45 g, 3.0 mmol) and thionyl chloride (5 mL) was

Table 6. Physical Properties of 1-Benzoyl Heterocycles

no.	−X−Y−	R	mp (°C)	formula[a]
16a	−CH₂−	4-NO₂	88.5−89	C₁₆H₁₄N₂O₃
16b	−CH₂−	3-NO₂	134−135	C₁₆H₁₄N₂O₃
16c	−CH₂−[b]	2-NO₂	152−154	C₁₆H₁₄N₂O₃[c]
16d	−O−	4-NO₂	169−170	C₁₅H₁₂N₂O₄
16e	−N(Me)−	4-NO₂	brown powder	C₁₆H₁₅N₃O₃[c]
16f	−CH₂CH₂−	4-NO₂	150−151	C₁₇H₁₆N₂O₃
16g	−OCH₂−	4-NO₂	147−148	C₁₆H₁₄N₂O₄
16h	−CH₂O−	4-NO₂	199.5−200.5	C₁₆H₁₄N₂O₄
16i	−N(Me)CH₂−	4-NO₂	oil	C₁₇H₁₇N₃O₃[c]
16j	−CH₂N(Me)−[d]	4-NO₂	oil	C₁₇H₁₇N₃O₃[c]
16k	−CH₂CH₂CH₂−	4-NO₂	87−88.5	C₁₈H₁₈N₂O₃
16l	−CH(NMe₂)CH₂−	4-NO₂	139−141	C₁₉H₂₁N₃O₃
16m	−COCH₂−	4-NO₂	150−151	C₁₇H₁₄N₂O₄
17a	−CH₂−	4-NH₂	211−212	C₁₆H₁₆N₂O
17b	−CH₂−	3-NH₂	130−132	C₁₆H₁₆N₂O
17c	−CH₂−[b]	2-NH₂	yellow powder	C₁₆H₁₆N₂O[c]
17d	−O−	4-NH₂	192−193	C₁₅H₁₄N₂O₂
17e	−N(Me)−	4-NH₂	211−213	C₁₆H₁₇N₃O
17f	−CH₂CH₂−	4-NH₂	175−176.5	C₁₇H₁₈N₂O
17g	−OCH₂−	4-NH₂	163−165	C₁₆H₁₆N₂O₂·¹/₄H₂O
17h	−CH₂O−	4-NH₂	216.5−219	C₁₆H₁₆N₂O₂
17i	−N(Me)CH₂−	4-NH₂	160−162	C₁₆H₁₉N₃O
17j	−CH₂N(Me)−	4-NH₂	169−171	C₁₇H₁₉N₃O[c]
17k	−CH₂CH₂CH₂−	4-NH₂	177.5−179	C₁₈H₂₀N₂O
17l	−CH(NMe₂)CH₂−	4-NH₂	242−245	C₁₉H₂₃N₃O·HCl·³/₂H₂O
17m	−COCH₂−	4-NH₂	218−221	C₁₇H₁₆N₂O₂
30a	−COCH₂−	e	237−238	C₂₅H₂₂N₂O₃
30b	−COCH₂−	f	241−242	C₂₄H₁₉ClN₂O₃

[a] See Table 1 for an explanation of tabulated data. [b] See ref 29. [c] This compound was isolated, but not purified or analyzed before use in the next step. [d] See ref 17. [e] 4-[(2-Methylbenzoyl)amino]. [f] 4-[2-chlorobenzoyl)amino].

refluxed for 1 h. The solvent was removed in vacuo, and the residue was dissolved in toluene. The solvent was removed on a rotary evaporator and the evaporation with toluene repeated to remove all of the thionyl chloride. This acid chloride, dissolved in dichloromethane (5 mL), was added dropwise to a solution of **17a** (0.50 g, 2.0 mmol) and triethylamine (0.5 mL) in dichloromethane (45 mL) at 0−5 °C, and the reaction mixture was stirred for 2 h at room temperature. The mixture was poured into water and extracted with dichloromethane. The organic layers were dried over magnesium sulfate, and concentrated. Column chromatography in dichloromethane over silica gel afforded **20h** (0.52 g, 72%) as colorless needles: mp 203−204 °C; NMR (CDCl₃) δ 2.03 (quint, $J = 6.6$ Hz, 2H), 2.83 (t, $J = 6.6$ Hz, 2H), 3.89 (t, $J = 6.5$ Hz, 2H), 6.73 (d, $J = 7.9$ Hz, 1H), 6.88 (dd, $J = 7.2, 7.2$ Hz, 1H), 6.99 (ddd, $J = 7.3, 7.3, 1.1$ Hz, 1H), 7.15 (d, $J = 7.2$ Hz, 1H), 7.2−7.8 (m, 6H), 7.9−8.2 (m, 1H), 8.26 (s, 1H). Anal. (C₂₁H₁₈N₂O₂S) C, H, N.

1-[4-(Phenoxycarbonylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-benzazepine (29a). The title compound was prepared from phenyl chloroformate and **17f** by the procedure described for the preparation of **16a**. The product was recrystallized from ethyl acetate to give **29a** (23%) as a white solid: mp 199−201 °C; NMR (CDCl₃) δ 1.3−1.7 (m, 1H), 1.8−2.3 (m, 3H), 2.6−3.2 (m, 3H), 4.8−5.2 (m, 1H), 6.63 (d, $J = 7.2$ Hz, 1H), 6.8−7.5 (m, 13H). Anal. (C₂₄H₂₂N₂O₃) C, H, N.

1-(4-Benzenesulfonamidobenzoyl)-2,3,4,5-tetrahydro-1*H*-benzazepine (29b). The title compound was prepared from benzenesulfonyl chloride and **17f** by the procedure described for the preparation of **16a**. The product was recrystallized from methanol−ether to give **29b** (35%) as colorless prisms: mp 178−182.5 °C; NMR (CDCl₃) δ 1.3−1.65 (m, 1H), 1.7−2.2 (m, 3H), 2.55−3.2 (m, 3H), 4.96 (br d, $J = 13.5$ Hz, 1H), 6.53 (d, $J = 7.6$ Hz, 1H), 6.6−7.6 (m, 10H), 7.65 (d, $J = 7.2$ Hz, 2H), 7.89 (s, 1H). Anal. (C₂₃H₂₂N₂O₃S) C, H, N.

1-[4-(*N*-Phenylureido)benzoyl]-2,3,4,5-tetrahydro-1*H*-benzazepine (29c). To a solution of **17f** (0.80 g, 3.0 mmol)

in dichloromethane (20 mL) was added phenyl isocyanate (0.38 g, 3.2 mmol), and the solution was stirred for 0.5 h at room temperature. The solvent was removed, and the residue was crystallized with ethyl acetate to give **29c** (1.1 g, 95%) as a white solid: mp 244−245 °C; NMR (CDCl₃) δ 1.3−2.2 (m, 4H), 2.6−3.2 (m, 3H), 4.99 (br d, $J = 13.3$ Hz, 1H), 6.60 (d, $J = 7.6$ Hz, 1H), 6.7−7.5 (m, 12H), 8.10 (s, 1H), 8.13 (s, 1H). Anal. (C₂₄H₂₃N₃O₂) C, H, N.

5-(Dimethylamino)-1-[4-[(2-methylbenzoyl)amino]benzoyl]-2,3,4,5-tetrahydro-1*H*-benzazepine (31b). To a stirred solution of **17f** (51 g, 0.17 mol) and triethylamine (43 mL) in dichloromethane (700 mL) was added *o*-toluoyl chloride (32 mL, 0.25 mol) at 0−5 °C, and mixture was stirred for 0.5 h at 0−5 °C. The mixture was poured into water and extracted with dichloromethane. The organic layers were washed with water, dried over magnesium sulfate, and concentrated. Column chromatography (elution: 1−3%methanol/dichloromethane) followed by recrystallization from EtOH provided **31b** (39 g, 54%) as colorless prisms: mp 207−208 °C; NMR (measured at room temperature in DMSO-*d₆*) δ 1.0−3.7, 3.8−4.2, 4.7−5.1 (each m with two s at δ 2.14 and 2.36, total 16H), 6.6−7.9 (m, 12H), 10.2−10.5 (m, 1H): (measured at 120 °C in DMSO-*d₆*) δ 1.6−2.1 (m, 4H), 2.28 (s, 6H), 2.37 (s, 3H), 3.2−3.7 (m, 2H), 3.88 (br s, 1H), 6.81 (dd, $J = 6.2, 1.3$ Hz, 1H), 7.04 (ddd, $J = 6.1, 6.1, 1.3$ Hz, 1H), 7.16 (ddd, $J = 6.1, 6.1, 1.1$ Hz, 1H), 7.19−7.38 (m, 5H), 7.40 (d, $J = 6.2$ Hz, 2H), 7.51−7.59 (m, 2H), 9.82 (s, 1H). Anal. (C₂₇H₂₉N₃O₂) C, H, N.

5-(Methylamino)-1-[4-[(2-methylbenzoyl)amino]benzoyl]-2,3,4,5-tetrahydro-1*H*-benzazepine (31f). A mixture of **30a** (2.5 g, 6.3 mmol), 40% methylamine methanol solution (30 mL), molecular sieves (4A, 2.5 g), methanol (20 mL), and dimethylformamide (40 mL) was refluxed for 5 h. After cooling to room temperature, NaBH₄ (0.36 g, 9.4 mmol) was added to the mixture. The mixture was stirred for 1 h at room temperature, and the mixture was filtered through Celite and concentrated. The residue was poured into water and extracted with dichloromethane. The organic layers was washed with water, brine, dried over magnesium sulfate, and concen-

trated. Column chromatography in 10:1 dichloromethane–methanol over silica gel followed by recrystallization from dioxane yielded **31f** (2.0 g, 77%) as colorless prisms: mp 210–211 °C; NMR (CDCl$_3$) δ 1.1–3.3 (m with three s at δ 2.43, 2.56, and 2.46, 12H), 3.65–3.82 (m, 1 × $^1/_3$H), 3.95–4.14 (m, 1 × $^2/_3$H), 4.41–4.65 (m, 1 × $^2/_3$H), 5.01–5.26 (m, 1 × $^1/_3$H), 6.66 (d, J = 7.5 Hz, 1H), 6.90–7.72 (m, 12H). Anal. (C$_{26}$H$_{27}$N$_3$O$_2$·$^1/_4$H$_2$O) C, H, N.

Ethyl *N*-Methyl-*N*-[1-[4-[(2-methylbenzoyl)amino]benzoyl]-2,3,4,5-tetrahydro-5(1*H*)-benzazepinyl]aminoacetate (31j). A mixture of **31f** (1.6 g, 3.9 mmol), ethyl bromoacetate (0.44 mL, 4.4 mmol), potassium carbonate (0.60 g), and acetonitrile (20 mL) was refluxed for 3 h, and concentrated. The residue was poured into water and extracted with dichloromethane. The organic layers were dried over magnesium sulfate and concentrated. Column chromatography in 30:1 dichloromethane–methanol over silica gel followed by recrystallization from ethyl acetate–petroleum ether yielded **31j** (0.82 g, 41%) as colorless prisms: mp 167–168 °C; NMR (CDCl$_3$) δ 1.15–2.8 (m, with t at δ 1.30 (J = 7.2 Hz) and two s at δ 2.47 and 2.57, 13H), 3.2–3.7, 3.9–4.4, 4.9–5.2 (each m, with q at δ 4.21 (J = 7.2 Hz), 7H), 6.61 (d, J = 7.1 Hz, 1H), 6.8–7.6 (m, 11H), 7.62 (d, J = 7.7 Hz, 1H). Anal. (C$_{30}$H$_{33}$N$_3$O$_4$) C, H, N.

5-[*N*-(Cyanomethyl)methylamino]-1-[4-[(2-methylbenzoyl)amino]benzoyl]-2,3,4,5-tetrahydro-1*H*-benzazepine (31k). To a solution of **31f** (0.60 g, 1.5 mmol) in methanol (10 mL) was added glycolonitrile (50 wt % solution in water, 0.7 mL), and the mixture was refluxed for 6 h. After concentration, the residue was triturated with ethyl acetate. The resulting crystals were collected by filtration and recrystallized from acetonitrile to give **31k** (0.32 g, 49%) as colorless needles: mp 227–228 °C; NMR (CDCl$_3$) δ 1.1–4.2, 4.8–5.2 (each m, with two s at δ 2.48 and 2.58, 15H), 6.5–7.9 (m, 13H). Anal. (C$_{28}$H$_{28}$N$_4$O$_2$) C, H, N.

5-[(2-Amino-2-oxoethyl)methylamino]-1-[4-[(2-methylbenzoyl)amino]benzoyl]-2,3,4,5-tetrahydro-5(1*H*)-benzazepine (31l). A mixture of **31j** (0.60 g, 1.2 mmol) and ammonia (2 M solution in methanol, 20 mL) was heated in an autoclave at 100 °C for 8 h and concentrated. Column chromatography in 30:1 dichloromethane–methanol over silica gel afforded **31l** (0.40 g, 71%) as a colorless glass: NMR (CDCl$_3$) δ 1.3–3.6 (m with two s at δ 2.47 and 2.55, 13H), 3.8–4.2, 4.3–4.6, (m, 1H), 4.8–5.8 (m, 1H), 6.5–7.9 (m with d at δ 6.67 (J = 7.4 Hz), 15H). Anal. (C$_{28}$H$_{30}$N$_4$O$_3$·$^1/_2$H$_2$O) C, H, N.

5-(Acetoxyimino)-1-[4-[(2-methylbenzoyl)amino]benzoyl]-2,3,4,5-tetrahydro-1*H*-benzazepine (31m). A mixture of **30a** (10 g, 25 mmol), hydroxylamine hydrochloride (5.23 g, 75 mmol), and pyridine (100 mL) was refluxed for 2.5 h. After cooling to room temperature, acetic anhydride (100 mL) was added to the mixture and stirred for 3 h. The mixture was concentrated and poured into water and then extracted with dichloromethane. The organic layers were washed with aqueous cupric sulfate, brine, dried over magnesium sulfate, and concentrated. Column chromatography in 30:1 dichloromethane–methanol over silica gel followed by recrystallization from ethanol afforded **31m** (9.80 g, 86%) as colorless needles: mp 190–191 °C; NMR (CDCl$_3$) δ 1.5–2.2 (m, 2H), 2.28 (s, 3H), 2.47 (s, 3H), 2.76–3.10 (m, 2H), 3.15–3.8 (m, 1H), 4.46 (br s, 1H), 6.73 (dd, J = 7.2, 1.7 Hz, 1H), 7.1–7.5 (m, 10H), 7.56 (s, 1H), 7.64 (dd, J = 7.5, 1.6 Hz, 1H). Anal. (C$_{27}$H$_{25}$N$_3$O$_4$) C, H, N.

5-Amino-1-[4-[(2-methylbenzoyl)amino]benzoyl]-2,3,4,5-tetrahydro-1*H*-benzazepine (31n). A mixture of **31m** (7.7 g, 17 mmol), PtO$_2$ (0.7 g) and acetic acid (100 mL) was stirred at room temperature under hydrogen atmosphere (1 atm) for 5 h. The mixture was filtered through Celite and evaporated. The residue was dissolved in dichloromethane and this solution was washed with saturated NaHCO$_3$ and water, dried over magnesium sulfate, and concentrated. Column chromatography (elution: 5–10% methanol/dichloromethane) over silica gel followed by crystallization with ether afforded **31n** (6.5 g, 96%) as a white solid: mp 198.5–199.5 °C; NMR (CDCl$_3$) δ 1.2–2.6, 2.6–3.9, 4.15–4.9, 5.0–5.3 (each m with s at δ 2.47, total 12H), 6.66 (d, J = 7.6 Hz, 1H), 6.85–7.75 (m, 12H). Anal. (C$_{25}$H$_{25}$N$_3$O$_2$) C, H, N.

1-[4-[(2-Chlorobenzoyl)amino]benzoyl]-5-piperidyl-2,3,4,5-tetrahydro-1*H*-benzazepine (31o). To a stirred solution of **30b** (0.20 g, 0.48 mmol), piperidine (0.21 g, 2.4 mmol), Et$_3$N (0.35 mL, 2.5 mmol), and dichloromethane (10 mL) was added dropwise TiCl$_4$ (0.5 M solution in dichloromethane, 1.2 mL). The mixture was stirred at room temperature overnight. After removal of the solvent, the residue was dissolved in EtOH (10 mL). To the mixture was added NaBH$_4$ (22 mg, 0.58 mmol), and the mixture was stirred for 2 h at room temperature. The reaction mixture was poured into water and extracted with dichloromethane. The organic layers were washed with water, dried over magnesium sulfate, and concentrated. Column chromatography in 100:1 dichloromethane–methanol over silica gel followed by recrystallization from ethanol afforded **31o** (0.064 g, 28%) as a white solid: mp 236–239 °C; NMR (CDCl$_3$) δ 1.05–3.82, 3.95–4.22, 5.0–5.3 (each m, total 17H), 6.5–8.2 (m with d at δ 6.59 (J = 7.5 Hz), 12H). Anal. (C$_{29}$H$_{30}$ClN$_3$O$_2$) C, H, N.

5-(Dimethylamino)-1-[4-[(*N*-methyl-2-methylbenzoyl)amino]benzoyl]-2,3,4,5-tetrahydro-1*H*-benzazepine (31s). A solution of **31b** (1.0 g, 2.3 mmol) in dimethylformamide (30 mL) was treated with sodium hydride (60% dispersion in oil, 0.13 g) at room temperature and the mixture was stirred for 40 min. To this mixture was added dropwise a solution of methyl iodide (0.14 mL, 2.3 mmol) at 0–4 °C, and the mixture was stirred at room temperature for 2.5 h. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layers were washed with water, dried over magnesium sulfate, and concentrated. The residue was crystallized with ether–hexane to afford **31s** (0.91 g, 90%) as a white powder: mp 182–182.5 °C; NMR (CDCl$_3$) δ 1.2–2.45, 2.5–3.1, 3.1–3.65, 3.95–4.25, 4.85–5.15 (each m with three s at δ 2.01, 2.19, 2.38, total 19H), 6.3–7.65 (m, 12H). Anal. (C$_{28}$H$_{31}$N$_3$O$_2$·$^1/_4$H$_2$O) C, H, N.

5-(Acetylamino)-1-[4-[(2-methylbenzoyl)amino]benzoyl]-2,3,4,5-tetrahydro-1*H*-benzazepine (31q). To a stirred mixture of **31m** (0.27 g, 0.7 mmol) and pyridine (5 mL) was added acetic anhydride (5 mL), and the mixture was stirred at room temperature for 15 h. The reaction mixture was poured into ice–water. The resulting crystals were collected by filtration and recrystallized from ethanol to give **31q** (0.3 g, 44%) as colorless needles: mp 297–299 °C; NMR (DMSO-d_6) δ 1.4–3.1 (m with two s at δ 2.00 and 2.32, 10H), 3.7–4.0 (m, 1H), 4.3–4.7 (m, 1H), 4.9–5.4 (m, 1H), 6.53 (d, J = 7.9 Hz, 1H), 6.7–7.7 (m, 11H), 7.8–8.2 (m, 1H), 9.90 (br s, 1H). Anal. (C$_{27}$H$_{27}$N$_3$O$_3$·EtOH) C, H, N.

1-[4-[(2-Methylbenzoyl)amino]benzoyl]-5-(*N*-methylureido)-2,3,4,5-tetrahydro-1*H*-benzazepine (31r). A mixture of **31n** (0.60 g, 1.5 mmol), methyl isocyanate (0.18 mL, 3.1 mmol), and dichloromethane (10 mL) was stirred at room temperature overnight and concentrated. The residue was crystallized with dimethylformamide to give **31r** (0.10 g, 14%) as colorless prisms: mp 286–287 °C; NMR (DMSO-d_6) δ 1.2–3.4 (m with s at δ 2.32 and d at δ 2.61 (J = 4.6 Hz), 11H), 4.1–5.3 (m, 2H), 5.7–6.1 (m, 1H), 6.4–7.1 (m, 13H), 10.3 (s, 1H). Anal. (C$_{27}$H$_{28}$N$_4$O$_3$·$^3/_4$H$_2$O) C, H; N: calcd, 11.92; found, 12.41.

1-[4-[(2-Aminobenzoyl)amino]benzoyl]-5-(dimethylamino)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (31x). A mixture of **31w** (4.65 g, 10.2 mmol), platinum oxide (0.3 g), ethanol (100 mL), and water (4 mL) was stirred at 40–50 °C under hydrogen atmosphere (1 atm) for 3 h. The mixture was filtered through Celite to remove the catalyst which was rinsed with ethanol, and the filtrate was concentrated. Column chromatography (elution: 1–2% methanol/dichloromethane) followed by recrystallization from CHCl$_3$–AcOEt provided **31x** (3.24 g, 75%) as colorless prisms: mp 224–227 °C; NMR (CDCl$_3$) δ 1.0–2.8, 2.9–3.15, 3.4–3.7, 3.9–4.15, 4.9–5.25 (each m with two s at δ 2.17 and 2.42, total 13H), 5.46 (br s, 2H), 6.5–6.85 (m, 3H), 6.85–7.7 (m, 9H), 7.93 (br s, 1H). Anal. (C$_{24}$H$_{28}$N$_4$O$_2$) C, H, N.

1-[4-[[2-(Acetylamino)benzoyl]amino]benzoyl]-5-(dimethylamino)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (31y). To a stirred mixture of **31x** (0.90 g, 2.1 mmol) and dichloromethane (24 mL) was added acetic anhydride (0.30 mL, 3.15 mmol), and the mixture was stirred at room temperature for

3 h. The reaction mixture was poured into ice−water and basified with saturated aqueous $NaHCO_3$ and extracted with dichloromethane. The organic layers were washed with water, dried over magnesium sulfate, and concentrated. Column chromatography (elution: 1−2% methanol/dichloromethane) followed by recrystallization from $CHCl_3$−AcOEt provided **31y** (0.90 g, 90%) as colorless prisms: mp 226−229 °C; NMR ($CDCl_3$) δ 1.05−2.85, 2.9−3.15, 3.3−3.7, 3.9−4.25, 4.9−5.2 (each m with three s at δ 2.13, 2.18, and 2.44, total 16H), 6.5−6.85, 6.85−7.8 (each m, total 11H), 8.05−8.4 (m, 1H), 8.9−9.35 (m, 1H), 10.43, 10.52 (each s, total 1H). Anal. ($C_{28}H_{30}$-N_4O_3·$^1/_4H_2O$) C, H, N.

AVP Receptor Binding Assay. Procedures for the radioligand binding assays have been reported in detail.[22,23] The IC_{50} value is the concentration of compound which inhibits [^{3}H]-AVP binding by 50%. Assays performed in duplicate. Intraassay and interassay IC_{50} values for a given compound may vary less than 3% and less than 20%, respectively. For **31b** (OPC-31260) the $IC_{50} \pm$ SEM is $1.2 \pm 0.2 \times 10^{-6}$ M for V_{1a} receptors and $1.4 \pm 0.2 \times 10^{-8}$ M for V_2 receptors ($n = 3$).

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