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# Synthesis and biological activity of novel 4,4-difluorobenzazepine derivatives as non-peptide antagonists of the arginine vasopressin $V_{1A}$ receptor

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**Abstract**—To find potent and selective antagonists of the arginine vasopressin (AVP) $V_{1A}$ receptor, optimization studies of compounds structurally related to (*Z*)-*N*-{4′-[(4,4-difluoro-5-carbamoylmethylidene-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)carbonyl]phenyl}carboxamide were performed. The synthesis and pharmacological properties of these compounds are described. We first investigated the effect of the carboxamide moiety, and found that a 2-methylfuran-3-carbonyl group at this position increased $V_{1A}$ binding affinity and selectivity for the $V_{1A}$ receptor versus the $V_2$ receptor. The amino group of the 5-carbamoylmethylidene moiety was also examined, and a 4-piperidinopiperidino group was found to be optimal at this position. The hemifumarate of compound **12l** (YM218) was shown to exhibit potent binding affinity, $V_{1A}$ receptor selectivity, and in vivo antagonist activity.


## 1. Introduction

Arginine vasopressin (AVP) is a 9-amino acid polypeptide hormone that is released by the posterior pituitary gland and regulated by an intricate homeostatic mechanism that controls water balance.[1,2] AVP receptors are classified into three types, $V_{1A}$, $V_{1B}$, and $V_2$ receptors,[3–5] and the $V_{1A}$ receptor is found in blood vessels, platelets, the liver, and renal mesangial cells. AVP plays a role in various physiological effects, such as vasoconstriction, platelet aggregation, glycogenolysis, and the contraction of mesangial cells, all of which are mediated by the $V_{1A}$ receptor. Overproduction of AVP is thought to cause congestive heart failure, hypertension, liver disease, and kidney disease through binding to the $V_{1A}$ receptor,[6] and therefore $V_{1A}$ receptor antagonists may be useful for treatment of these diseases.

Non-peptide $V_{1A}$ receptor-selective antagonists OPC-21268 (**1**), SR49059 (**2**), and triazole derivatives (**3**) have been reported (Fig. 1),[7–12] and we have previously reported $V_{1A}$ receptor antagonists (**4**–**6**) containing the (*Z*)-4,4-difluoro-5-carbamoylmethylidene-2,3,4,5-tetrahydro-1*H*-1-benzazepine moiety (Fig. 2).[13,14] However, the selectivity of the 2-ethoxybenzoyl derivatives (**4**, **5**) for binding to the $V_{1A}$ receptor versus the $V_2$ receptor was insufficient, and the 2-(2-ethyl-1*H*-imidazol-1-yl)benzoyl derivative (**6**) showed decreased $V_{1A}$ receptor selectivity for the cloned human receptor, compared to the rat receptor. Conversion of the $R^1$ substituents into groups containing hetero atoms, such as 2-alkoxybenzoyl- or 2-(2-ethyl-1*H*-imidazol-1-yl)benzoyl, gave compounds with potent binding affinity and selectivity for the $V_{1A}$ receptor, and we found that the substituent at the 2-position of the benzoyl group at $R^1$ is more important for

*Keywords*: YM218; Arginine vasopressin; $V_{1A}$ receptor selective antagonist; 2-Methylfuran-3-carbonyl group.
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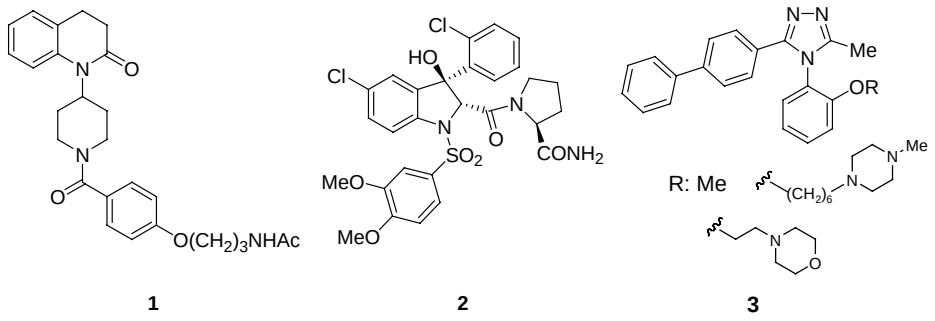



**Figure 1.** Structure of known non-peptide arginine vasopressin $V_{1A}$ receptor selective antagonist.

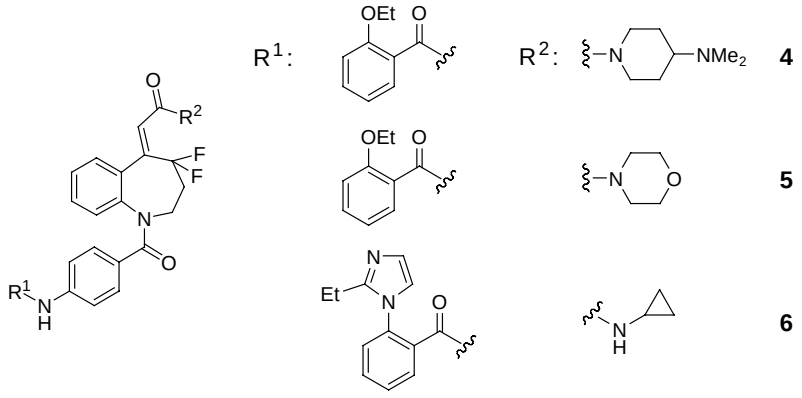



**Figure 2.** Structure of 4,4-difluorobenzazepine derivatives.

potent $V_{1A}$ antagonist activity, compared to those at the 3- or 4-positions of the benzoyl group.[15] These results suggest that introduction of substituents at the $R^1$ position containing both a hetero atom and a substituent *ortho* to the carbonyl group might give compounds with potent binding affinity and selectivity for the $V_{1A}$ receptor. Based on this hypothesis, we chose a five-membered heterocyclic ring with a methyl group *ortho* to the carbonyl group. Moreover, we optimized the $R^2$ position of the 5-carbonylmethylidene moiety and found a series of compounds that were highly potent and selective $V_{1A}$ receptor antagonists. In this paper, we describe the structure–activity relationships (SAR) and antagonist activities of this series of compounds.

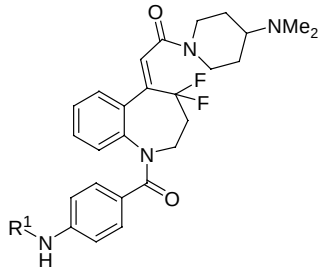
## 2. Chemistry

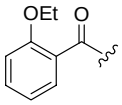
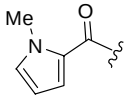
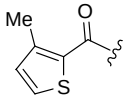
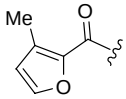
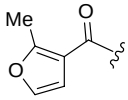
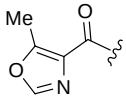
The general synthetic pathways for the compounds listed in Tables 1 and 2 are shown in Scheme 1. The key intermediate, (*Z*)-methyl [1-(4-aminobenzoyl)-4,4-difluoro-2,3,4,5-tetrahydro-1*H*-1-benzazepine-5-ylidene]acetate (**7**), was synthesized by condensation of **8**[16] with 4-nitrobenzoyl chloride to give the nitrobenzoyl derivative (**9**). The nitro group of **9** was reduced with tin(II) chloride[17] to obtain the aminobenzoyl derivative without reduction of the methylidene group. The heterocyclic acid chlorides were reacted with compound **7** to give methyl ester derivatives **10a**–**e**, which were treated with 1 M NaOH to give the acetic acid derivatives (**11a**–**e**). Condensation of **11a**–**e** and various amines in the presence of 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (WSC•HCl) and 1-hydroxybenzotriazole (HOBt) gave the target amide derivatives **12a**–**n**. Among these compounds **12a**–**d**, **g**, **j**–**l**, and **n** were treated with a 4 M solution of HCl in ethyl acetate and obtained as HCl salts.

## 3. Results and discussion

The influence of the $R^1$ position on $V_{1A}$ selectivity in a series of five-membered heterocyclic carbonyl derivatives is shown in Table 1. The 1-methyl-1*H*-pyrrole-2-carbonyl derivative (**12a**) and 3-methylthiophen-2-carbonyl derivative (**12b**) exhibited a similar or more potent $V_{1A}$ binding affinity, compared to that of the 2-ethoxybenzoyl derivative (**4**). The 3-methylfuran-2-carbonyl derivative (**12c**) exhibited potent $V_{1A}$ receptor binding affinity and 120-fold $V_{1A}$ selectivity against the $V_2$ receptor. These results suggest that the oxygen atom is important for high $V_{1A}$ receptor selectivity in both five-membered heterocyclic carbonyl derivatives and 2-alkoxybenzoyl derivatives. The 2-methylfuran-3-carbonyl derivative (**12d**) exhibited the most potent affinity among the heterocyclic carbonyl derivatives and showed a 331-fold selectivity for the $V_{1A}$ versus the $V_2$ receptor. These results suggest that $V_{1A}$ binding affinity and selectivity are influenced by both an electronic effect and the position of the oxygen atom. However, the 5-methyl-1,3-oxazole-4-carbonyl derivative (**12e**), which has an oxygen atom in the same position as **12d**, showed decreased binding affinity compared to **12d**.

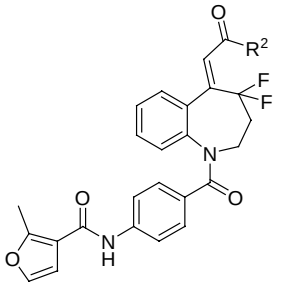
**Table 1.** Receptor binding affinities of the five-membered heterocyclic carbonyl derivatives

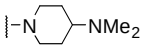
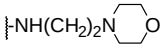
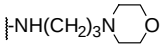
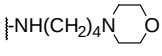
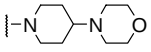
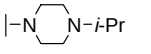
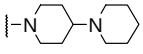
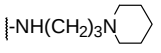
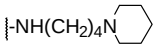


| Compound | $R^1$ | Binding affinity $K_i$ (nM) | | Selectivity $K_i$ ratio |
|---|---|---|---|---|
| | | $V_{1A}$[a] | $V_2$[b] | $V_2/V_{1A}$[c] |
| **4** |  | 0.603 | 22.4 | 37 |
| **12a**·HCl |  | 0.398 | 17.8 | 45 |
| **12b**·HCl |  | 0.562 | 6.92 | 12 |
| **12c**·HCl |  | 0.263 | 31.6 | 120 |
| **12d**·HCl |  | 0.102 | 33.9 | 331 |
| **12e** |  | 0.661 | 91.2 | 138 |

[a] Rat liver membranes were used. $K_i$ values obtained from two independent experiments performed in duplicate.
[b] Rat kidney membranes were used. $K_i$ values obtained from two independent experiments performed in duplicate.
[c] $V_2/V_{1A}$ shows the selectivity for binding to the $V_{1A}$ receptor versus the $V_2$ receptor.

**Table 2.** Receptor binding affinities of the 2-methylfuran-3-carbonyl derivatives with various amino groups

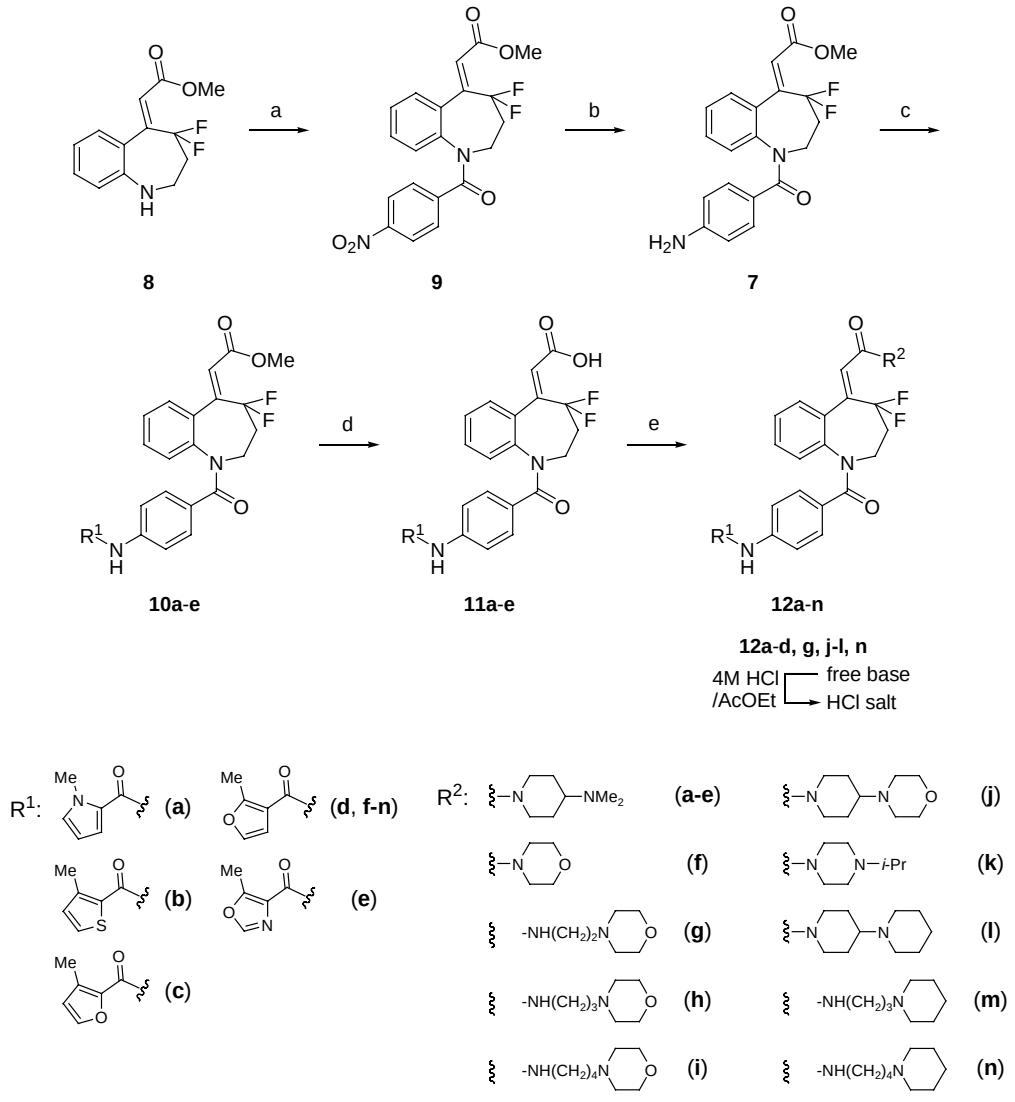


| Compound | $R^2$ | Binding affinity $K_i$ (nM) | | Selectivity $K_i$ ratio |
|---|---|---|---|---|
| | | $V_{1A}$[a] | $V_2$[b] | $V_2/V_{1A}$[c] |
| **12d** |  | 0.102 | 33.9 | 331 |
| **12f** |  | 1.41 | 7.94 | 6 |
| **12g**·HCl |  | 0.562 | 3.02 | 5 |
| **12h** |  | 0.331 | 10.5 | 32 |
| **12i** |  | 0.145 | 17.0 | 118 |
| **12j**·HCl |  | 1.41 | 55.0 | 39 |
| **12k**·HCl |  | 1.51 | 41.7 | 28 |
| **12l**·HCl |  | 0.112 | 42.7 | 380 |
| **12m** |  | 0.214 | 6.03 | 28 |
| **12n**·HCl |  | 0.339 | 8.13 | 24 |

[a] Refer to Table 1.
[b] Refer to Table 1.
[c] Refer to Table 1.

Since five-membered heterocyclic carbonyl substituents increased $V_{1A}$ selectivity, compared to the 2-alkoxybenzoic acid moiety, a 2-methylfuran-3-carbonyl substituent was chosen for the $R^1$ position. Further optimization of the amino group at $R^2$ on the 5-carbonylmethylidene moiety was then performed, as shown in Table 2. In a preceding paper,[13] the introduction of morpholino and 4-dimethylaminopiperidino groups at this position gave compounds with potent binding affinity and selectivity for the $V_{1A}$ receptor. Therefore, we first synthesized and evaluated the morpholino derivative (**12f**), but this compound showed only a 6-fold $V_{1A}$ selectivity against $V_2$. Introduction of an alkylene chain between the carboxamide and morpholino groups gave compounds **12g–i**, which showed increased $V_{1A}$ receptor binding affinity with increasing alkylene chain length: $C_4$ (**12i**) > $C_3$ (**12h**) > $C_2$ (**12g**) > none (**12f**). The $V_{1A}$ versus $V_2$ receptor selectivity also increased with an increased alkylene chain length: $C_4$ (**12i**) > $C_3$ (**12h**) > $C_2$ (**12g**). The cyclic derivative ($C_3$, 4-morpholinopiperidino, **12j**) showed similar $V_{1A}$ selectivity to the open chain derivative ($C_3$, **12h**). These results suggest that a basic nitrogen atom and a suitable alkylene chain length between the carboxamide and the basic nitrogen atom are required at the $R^2$ position to obtain the desired properties.

Among compounds with 4-dimethylaminopiperidino-type substituents, the 4-isopropyl-1-piperazinyl deriva-




**Scheme 1.** Reagents and conditions: (a) 4-nitrobenzoylchloride, $Et_3N$, $CH_2Cl_2$; (b) $SnCl_2$, AcOEt; (c) 1—heterocyclic carboxylic acid, $(COCl)_2$, DMF, THF; 2—$R^1$-Cl, pyridine, acetonitrile; (d) 1—1 M NaOH, MeOH; 2—1 M HCl; (e) amine, HOBt, WSC·HCl, $CH_2Cl_2$, acetonitrile.

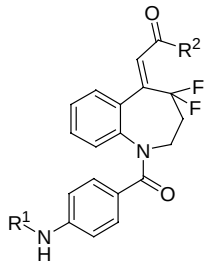
tive (**12k**) showed decreased $V_{1A}$ selectivity compared to **12d**. In contrast, the 4-piperidinopiperidino derivative (**12l**) exhibited one of the highest affinities and showed 380-fold selectivity for the $V_{1A}$ receptor versus the $V_2$ receptor. In comparing **12l** with **12d** and **12j**, it appears that the electronegative effect of the oxygen atom in the morpholino group (**12j**) decreased the $V_{1A}$ receptor binding affinity and selectivity. Based on the SAR study of derivatives **12i** and **12l**, open chain derivatives with piperidine (**12m**, **12n**) were chosen for synthesis and evaluation. However, although compounds **12m** and **12n** showed high affinities for the $V_{1A}$ receptor, their $V_{1A}$ selectivity was insufficient.

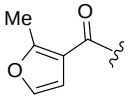
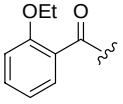
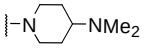
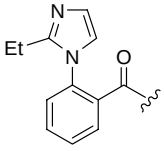
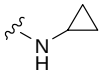
The binding of compound **12l** with cloned human $V_{1A}$ ($hV_{1A}$) and $V_2$ ($hV_2$) receptors was examined (Table 3), since this compound showed potent binding affinity and high selectivity for the rat $V_{1A}$ receptor. Compound **12l** exhibited similarly high binding affinity and selectivity for the human $V_{1A}$ receptor, showed increased $V_{1A}$ selectivity compared to **4**, **5**, and **6**, and exhibited the most selective $V_{1A}$ receptor antagonist activity encountered in studies of 4,4-difluorobenzazepine derivatives.

The in vivo $V_{1A}$ receptor antagonist activity was evaluated following intravenous administration of compound **12l** to pithed rats. The compound showed dose-dependent antagonism of an AVP (30 mU/kg)-induced increase in diastolic blood pressure (DBP) via the $V_{1A}$ receptor, with an $ID_{50}$ value of 0.0035 mg/kg. The time course of antagonism of the AVP-induced increase in DBP was also monitored after oral administration of **12l** (0.3, 1, and 3 mg/kg) to conscious rats (Fig. 3). Compound **12l** dose-dependently antagonized the AVP-induced increase in DBP, and its effect lasted for at least 8 h at doses of 3 mg/kg. In contrast, oral administration (0.3–3 mg/kg) of **12l** did not increase urine excretion in conscious rats. These results show that **12l** is a selective and orally active antagonist for the $V_{1A}$ receptor.

To investigate the basis of the potent binding affinity and selectivity for the $V_{1A}$ receptor and the strong $V_{1A}$

**Table 3.** AVP binding affinities with cloned human $V_{1A}$ ($hV_{1A}$) and $V_2$ ($hV_2$) receptors of compounds **12l**, **4**, **5**, and **6**



| Compound | $R^1$ | $R^2$ | Binding affinity $K_i$ (nM) | | Selectivity $K_i$ ratio |
|---|---|---|---|---|---|
| | | | $hV_{1A}$[a] | $hV_2$[b] | $hV_2/hV_{1A}$[c] |
| **12l**·HCl |  | | 0.224 | 79.4 | 354 |
| **4**·HCl |  |  | 0.891 | 45.7 | 51 |
| **5** | |  | 0.158 | 7.08 | 44 |
| **6** |  |  | 1.00 | 141 | 140 |

[a] The cloned human $V_{1A}$ receptor, which was stably expressed in CHO cells, was used. $K_i$ values obtained from two independent experiments performed in duplicate.

[b] The cloned human $V_2$ receptor, which was stably expressed in CHO cells, was used. $K_i$ values obtained from two independent experiments performed in duplicate.

[c] $hV_2/hV_{1A}$ shows the selectivity for binding to the cloned human $V_{1A}$ receptor versus the cloned human $V_2$ receptor.

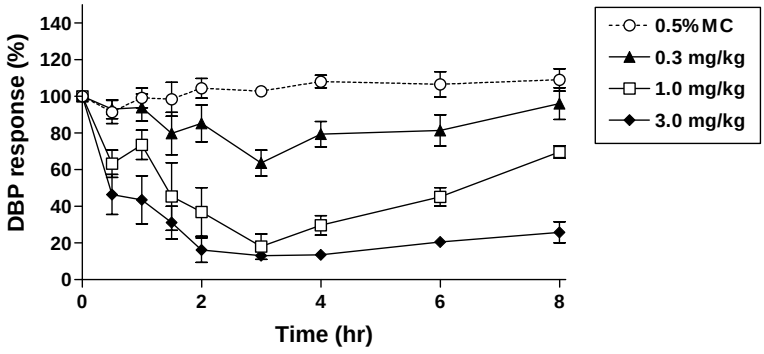



**Figure 3.** Inhibition of the peak pressor responses induced by AVP (30 mU/kg, iv) in conscious rats by oral administration of **12l**. Values represent means ± SEM of six independent experiments.

antagonist activity exhibited by compound **12l**, the stereochemical configuration of **12l** was examined. According to Hassner and Amit[18] *N*-acylbenzazepine, which forms the central skeleton of **12l**, has the structure shown in Figure 4 (**13**) at room temperature. The electrons on the nitrogen atom of the amide bond are located largely on the carbonyl oxygen atom, giving a double-bond character to the C–N amide bond of *N*-acylbenzazepine, and the carbonyl oxygen atom and the equatorial hydrogen ($H_e$) are in a *cis*-configuration. $^1$H NMR spectroscopy showed that the carbonyl oxygen atom was coplanar with $H_e$, and $H_e$ showed a downfield shift (ca. δ 4.8–5.0 ppm) relative to the position of the axial hydrogen ($H_a$) (ca. δ 2.7–3.0 ppm). Correspondence of the $^1$H NMR spectrum of *N*-acylbenzazepine[18] with that for compound **12l** ($H_e$: δ 4.86 ppm, $H_a$: δ 3.17 ppm) was observed, and therefore it was concluded that compound **12l** has the same stereochemical configuration as **13**.

Superimposition of **12l** with a model AVP structure was then performed. The X-ray crystal structure of AVP has

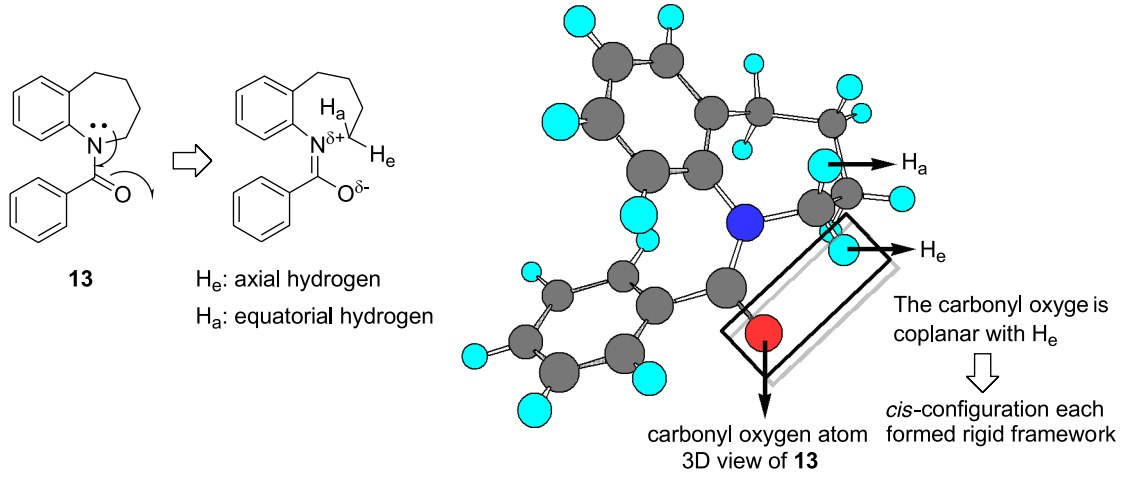



**Figure 4.** Stereochemical configuration of *N*-acylbenzazepine.

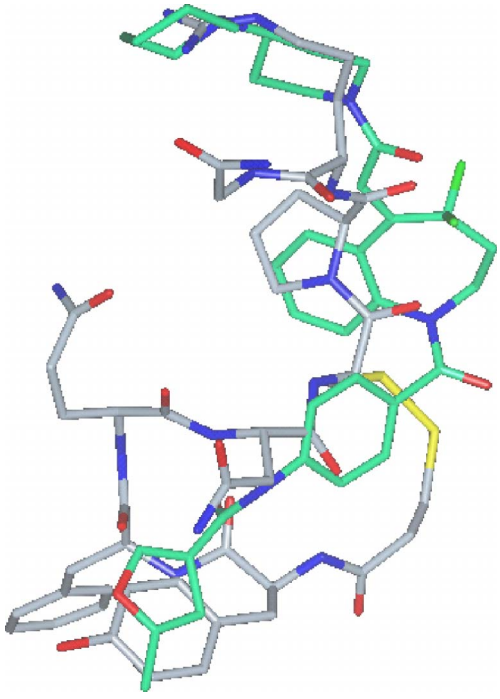


**Figure 5.** Superimposition of compound **12l** with a model AVP structure.

not been reported, and therefore the X-ray structure of oxytocin,[19] which has a similar cyclic structure to AVP and is also secreted from the posterior pituitary gland, was used as a 3D template incorporating the amino-acid sequence of AVP. The SYBYL[20] program was used to examine the 3D structures and to match AVP to **12l**. Superimposition was performed using the GASP[21] program, which permits overlap of hydrogen bonds and hydrophobic structures. The two terminal groups of **12l**, the 2-methylfuran-3-carbonyl moiety and the 4-piperidinopiperidino moiety, were superimposable with Tyr and Arg residues of AVP, respectively (Figs. 5 and 6). Based on these results, overlap between the oxygen atom of the 2-methylfuran-3-carbonyl moiety and the hydroxyl group of the Tyr residue, and between the basic nitrogen atom of the 4-piperidinopiperidino moiety and the guanidino group of the Arg residue was thought to contribute to the potent $V_{1A}$ binding affinity and selectivity. A superimposition study of a $V_{1A}/V_2$ dual antagonist and AVP has been reported by Cho et al.,[22] and overlap of the antagonist with the AVP Tyr, Phe, and Arg residues was proposed. Our results suggest that potent binding affinity and selectivity for the $V_{1A}$ receptor are dependent on overlap with the Tyr and Arg residues of AVP for compounds with *N*-acylbenzazepine in the central skeleton.

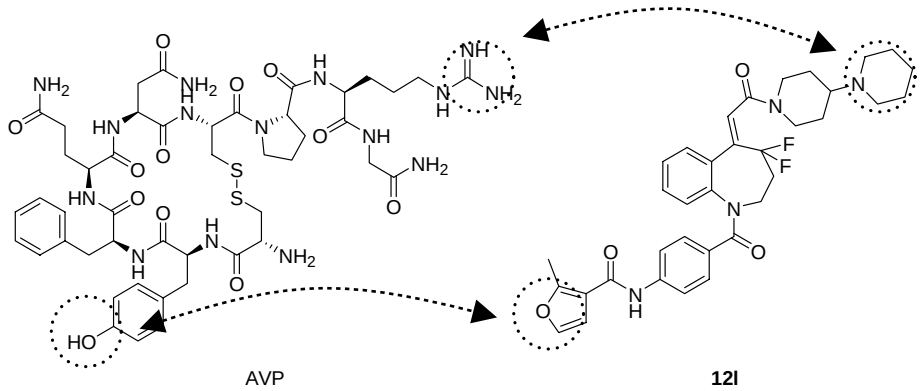



**Figure 6.** Correlation of functional groups between AVP and compound **12l**.

## 4. Conclusion

In this report, we have described the synthesis of (*Z*)-*N*-{4′-[(4,4-difluoro-5-carbamoylmethylidene-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)carbonyl]phenyl}carboxamide derivatives and evaluated their pharmacological properties, in order to obtain a potent and selective antagonist for the $V_{1A}$ receptor. The introduction of furancarbonyl groups on the carboxamide moiety ($R^1$ position) enhanced $V_{1A}$ binding affinity and selectivity, and basic substituents with a suitable spacer on the 5-carbonylmethylidene moiety ($R^2$ position) were essential for $V_{1A}$ selectivity. In particular, (*Z*)-*N*-[4′-(4,4-difluoro-5-[2-oxoethylidene-2-({4-piperidinopiperidino)]-2,3,4,5-tetrahydro-11-benzazepin-1-yl}carbonyl)phenyl]-2-methylfuran-3-carboxamide monohydrochloride (**12l**) exhibited potent binding affinity and $V_{1A}$ receptor selectivity across species, and also showed potent in vivo activities. The hemifumarate of **12l** is undergoing clinical trials as YM218[23,24] and is expected to be clinically applicable to diseases such as congestive heart failure and hypertension.

## 5. Experimental

### 5.1. General

$^1$H NMR spectra were obtained on a JNM-400 spectrometer, and the chemical shifts are expressed in δ (ppm) values with tetramethylsilane as an internal standard. Abbreviations of $^1$H NMR signal patterns are as follows: s, singlet; d, doublet; t, triplet; m, multiplet; and br, broad peak. Mass spectra were obtained on a JEOL JMS-DX300 mass spectrometer (low-resolution mass spectrometry) and JEOL JMS-700T mass spectrometer (high-resolution mass spectrometry). Elemental analysis was performed with a Yanaco MT-5. Column chromatography on silica gel was performed with Merck KGaA Silica gel 60 (0.040–0.063 mm).

### 5.2. (*Z*)-Methyl [4,4-difluoro-1-(4-nitrobenzoyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine-5-ylidene]acetate (9).

To an ice-cooled mixture of **8**[16] (2.15 g, 8.50 mmol) and triethylamine (1.13 g, 11.1 mmol) in $CH_2Cl_2$ (20 mL) was added 4-nitrobenzoyl chloride (1.90 g, 10.2 mmol), and the mixture was stirred for 12 h at room temperature and then extracted with ethyl acetate (AcOEt). The organic layer was washed with 1 M HCl, 1 M NaOH, and brine, and then dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on a silica gel column using $CHCl_3$ as the eluent and recrystallized from hexane–AcOEt to give 2.67 g (6.64 mmol, 78%) of **9** as a colorless powder. $^1$H NMR ($CDCl_3$) δ: 2.73 (2H, m), 3.81 (3H, s), 4.35 (1H, m), 4.95 (1H, br), 6.62 (1H, m), 7.25 (1H, m), 7.33 (1H, m), 7.48 (3H, m), 8.00 (1H, m), 8.10 (2H, m). EI MS *m*/*z* $(M)^+$ 402.

### 5.3. (*Z*)-Methyl [1-(4-aminobenzoyl)-4,4-difluoro-2,3,4,5-tetrahydro-1*H*-1-benzazepine-5-ylidene]acetate (7)

To a solution of **9** (1.00 g, 2.49 mmol) in AcOEt (20 mL) was added $SnCl_2$ (3.07 g, 16.2 mmol) at room temperature, and the mixture was refluxed for 5 h. After being cooled at 0 °C, the resulting mixture was made alkaline with 1 M NaOH and extracted with AcOEt. The organic layer was dried over anhydrous $K_2CO_3$ and concentrated in vacuo. The residue was recrystallized from hexane–$CHCl_3$ to give 0.782 g (2.10 mmol, 84%) of **7** as a colorless powder. $^1$H NMR ($CDCl_3$) δ: 2.66 (2H, m), 3.81 (3 H, s), 4.24 (1H, m), 4.95 (1H, br), 6.45 (2H, m), 6.76 (1H, m), 7.17 (2H, m), 7.24 (2H, m), 7.42 (3H, m), 7.95 (1H, m). EI MS *m*/*z* $(M)^+$ 372.

### 5.4. General procedure for the preparation of compounds 10a–e

**5.4.1. (*Z*)-Methyl {4,4-difluoro-1-[4-(1-methylpyrrole-2-carbonylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine-5-ylidene}acetate (10a).** To an ice-cooled mixture of 1-methylpyrrole-2-carboxylic acid (2.75 g, 22.0 mmol) and a catalytic amount of dimethylformamide (DMF) in tetrahydrofuran (30 mL) was added oxalyl chloride (3.05 g, 24.0 mmol). The mixture was stirred at room temperature for 3 h, diluted with $CHCl_3$, and concentrated in vacuo to give a corresponding acid chloride as a colorless powder. The acid chloride was used in the next reaction without further purification. To an ice-cooled mixture of **7** (7.45 g, 20.0 mmol) and pyridine (2 mL) in $CH_3CN$ (80 mL) was added a solution of acid chloride in $CH_3CN$ (20 mL). The mixture was stirred at room temperature for 8 h and then concentrated in vacuo. The residue was diluted with AcOEt. The organic layer was washed with a saturated aqueous solution of $Na_2CO_3$, 1 M HCl, and brine, and then dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude product was chromatographed on silica gel and eluted with hexane–AcOEt (60:40) to give 5.93 g (12.4 mmol, 62%) of **10a** as a colorless powder. $^1$H NMR ($CDCl_3$) δ: 2.28–2.82 (2H, m), 3.24 (1H, m), 3.83 (3H, s), 3.93 (3H, s), 5.04 (1H, m), 6.11 (1H, m), 6.19 (1H, s), 6.66 (1H, m), 6.72 (1H, d, *J* = 8.3 Hz), 6.77 (1H, m), 7.08–7.18 (3H, m), 7.23 (1H, t, *J* = 7.8 Hz), 7.36–7.40 (3H, m), 7.65 (1H, s). EI MS *m*/*z* $(M)^+$ 479.

**5.4.2. (*Z*)-Methyl {4,4-difluoro-1-[4-(3-methylthiophene-2-carbonylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine-5-ylidene}acetate (10b).** 90% yield. $^1$H NMR ($CDCl_3$) δ: 2.42 (1H, m), 2.55 (3H, s), 2.68 (1H, m), 3.26 (1H, m), 3.83 (3H, s), 5.05 (1H, m), 6.19 (1H, s), 6.72 (1H, d, *J* = 7.9 Hz), 6.93 (1H, d, *J* = 4.9 Hz), 7.11 (1H, t, *J* = 7.9 Hz), 7.16 (2H, d, *J* = 8.5 Hz), 7.24 (1H, t, *J* = 7.3 Hz), 7.32 (1H, d, *J* = 4.9 Hz), 7.40 (2H, d, *J* = 7.3 Hz), 7.49 (1H, d, *J* = 8.5 Hz). FAB MS *m*/*z* $(M+H)^+$ 497.

**5.4.3. (*Z*)-Methyl {4,4-difluoro-1-[4-(3-methylfuran-2-carbonylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine-5-ylidene}acetate (10c).** 86% yield. $^1$H NMR ($CDCl_3$) δ: 2.22–2.80 (2H, m), 2.41 (3H, s), 3.23 (1H, m), 3.83 (3H, s), 5.05 (1H, m), 6.19 (1H, s), 6.38 (1H, s), 6.71 (1H, d, *J* = 7.3 Hz), 7.10 (1H, dd, *J* = 7.3, 7.8 Hz), 7.15 (2H, d, *J* = 8.8 Hz), 7.23 (1H, dd, *J* = 7.3, 7.8 Hz), 7.34–7.38 (3H, m), 7.44 (1H, s), 7.46 (1H, s), 8.02 (1H, s). FAB MS *m*/*z* $(M+H)^+$ 481.

**5.4.4. (*Z*)-Methyl {4,4-difluoro-1-[4-(2-methylfuran-3-carbonylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine-5-ylidene}acetate (10d).** 87% yield. $^1$H NMR

($CDCl_3$) δ: 2.20–2.72 (2H, m), 2.61 (3H, s), 3.24 (1H, m), 3.83 (3H, s), 5.05 (1H, m), 6.18 (1H, s), 6.49 (1H, s), 6.70 (1H, d, $J$ = 7.3 Hz), 7.07–7.12 (4H, m), 7.22 (1H, dd, $J$ = 7.3, 7.8 Hz), 7.27 (1H, dd, $J$ = 7.3, 7.8 Hz), 7.35–7.45 (3H, m). FAB MS $m/z$ $(M+H)^+$ 481.

**5.4.5. (*Z*)-Methyl {4,4-difluoro-1-[4-(5-methyloxazole-4-carbonylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine-5-ylidene}acetate (10e).** 71% yield. $^1H$ NMR ($CDCl_3$) δ: 2.25–2.80 (2H, m), 2.67 (3H, s), 3.84 (3H, s), 5.05 (1H, m), 6.38 (1H, s), 6.71 (1H, d, $J$ = 7.3 Hz), 6.95–7.40 (4H, m), 7.45 (2H, d, $J$ = 7.8 Hz), 7.50 (2H, d, $J$ = 7.8 Hz), 7.71 (1H, s), 8.77 (1H, s). FAB MS $m/z$ $(M+H)^+$ 482.

### 5.5. General procedure for the preparation of compounds 11a–e

**5.5.1. (*Z*)-{4,4-Difluoro-1-[4-(1-methylpyrrole-2-carbonylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine-5-ylidene}acetic acid (11a).** The mixture of compounds **11a** (0.96 g, 2.00 mmol) in methanol (MeOH, 10 mL) and 1 M NaOH (4 mL) was stirred at room temperature for 7 h and then concentrated in vacuo. The residue was acidified with 1 M HCl (10 mL) under cooling conditions, and the solution was extracted with $CHCl_3$. The organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was recrystallized from hexane–AcOEt to give 0.72 g (1.54 mmol, 77%) of **11a** as a colorless powder. $^1H$ NMR (DMSO-$d_6$) δ: 2.35–2.82 (2H, m), 3.21 (1H, m), 3.94 (3H, s), 5.04 (1H, m), 6.10 (1H, m), 6.23 (1H, s), 6.70 (1H, d, $J$ = 8.7 Hz), 6.76 (1H, s), 6.87 (1H, m), 7.07–7.17 (3H, m), 7.22 (1H, t, $J$ = 7.8 Hz), 7.37 (2H, d, $J$ = 7.8 Hz), 7.50 (2H, d, $J$ = 8.7 Hz), 8.72 (1H, s). FAB MS $m/z$ $(M+H)^+$ 466.

**5.5.2. (*Z*)-{4,4-Difluoro-1-[4-(3-methylthiophene-2-carbonylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine-5-ylidene}acetic acid (11b).** 96% yield. $^1H$ NMR (DMSO-$d_6$) δ: 2.25–2.89 (2H, m), 2.53 (3H, s), 3.24 (1H, m), 5.04 (1H, m), 6.23 (1H, s), 6.71 (1H, d, $J$ = 7.8 Hz), 6.92 (1H, d, $J$ = 4.9 Hz), 7.12 (1H, t, $J$ = 7.8 Hz), 7.15 (2H, d, $J$ = 8.7 Hz), 7.23 (1H, t, $J$ = 7.3 Hz), 7.33 (1H, d, $J$ = 4.9 Hz), 7.38 (1H, d, $J$ = 7.3 Hz), 7.47 (2H, d, $J$ = 8.7 Hz), 8.40 (1H, s). FAB MS $m/z$ $(M+H)^+$ 483.

**5.5.3. (*Z*)-{4,4-Difluoro-1-[4-(3-methylfuran-2-carbonylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine-5-ylidene}acetic acid (11c).** 81% yield. $^1H$ NMR (DMSO-$d_6$) δ: 2.28–2.84 (2H, m), 2.41 (3H, s), 3.23 (1H, m), 5.06 (1H, m), 6.23 (1H, s), 6.39 (1H, s), 6.70 (1H, d, $J$ = 7.3 Hz), 7.07 (1H, dd, $J$ = 7.3, 7.8 Hz), 7.15 (2H, d, $J$ = 8.8 Hz), 7.22 (1H, dd, $J$ = 7.3, 7.8 Hz), 7.34–7.39 (3H, m), 7.48 (1H, s), 7.50 (1H, s), 8.33 (1H, s). FAB MS $m/z$ $(M+H)^+$ 467.

**5.5.4. (*Z*)-{4,4-Difluoro-1-[4-(2-methylfuran-3-carbonylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine-5-ylidene}acetic acid (11d).** 68% yield. $^1H$ NMR (DMSO-$d_6$) δ: 2.34–2.67 (2H, m), 2.50 (3H, s), 3.33 (1H, m), 4.87 (1H, m), 6.65 (1H, s), 6.81 (1H, d, $J$ = 7.3 Hz), 7.00 (1H, s), 7.05–7.15 (3H, m), 7.27 (1H, dd, $J$ = 7.3, 7.8 Hz), 7.37 (1H, dd, $J$ = 7.3, 7.8 Hz), 7.54–7.58 (3H, m), 9.74 (1H, s), 13.19 (1H, br). FAB MS $m/z$ $(M+H)^+$ 467.

**5.5.5. (*Z*)-{4,4-Difluoro-1-[4-(5-methyloxazole-4-carbonylamino)benzoyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine-5-ylidene}acetic acid (11e).** 87% yield. $^1H$ NMR (DMSO-$d_6$) δ: 2.25–2.80 (2H, m), 2.60 (3H, s), 3.23 (1H, m), 5.05 (1H, m), 6.33 (1H, s), 6.70 (1H, d, $J$ = 7.3 Hz), 6.85 (1H, m), 6.95–7.40 (3H, m), 7.45 (2H, d, $J$ = 7.8 Hz), 7.66 (2H, d, $J$ = 7.8 Hz), 8.42 (1H, s), 10.05 (1H, s). FAB MS $m/z$ $(M+H)^+$ 468.

### 5.6. General procedure for the preparation of compounds 12a–n

**5.6.1. (*Z*)-*N*-[4′-({4,4-Difluoro-5-[2-(4-dimethylaminopiperidino)-2-oxoethylidene]-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl}carbonyl)phenyl]-1-methylpyrrole-2-carboxamide monohydrochloride (12a).** To an ice-cooled mixture of **11a** (0.592 mmol) and 1-hydroxybenzotriazole (0.710 mmol) in $CH_2Cl_2$ (10 mL) and $CH_3CN$ (10 mL) was added 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (0.710 mmol) in $CH_2Cl_2$ (10 mL), and the mixture was stirred at room temperature for 1 h. After being cooled at 0 °C, 4-dimethylaminopiperizine (0.710 mmol) was added, and the mixture was stirred overnight at room temperature. To the mixture was added 1 M NaOH, which was then extracted with $CHCl_3$. The organic layer was dried over anhydrous $K_2CO_3$ and concentrated in vacuo. The residue was chromatographed on a silica gel column using $CHCl_3$–MeOH (95:5) as the eluent to give a free amine. This resulting amine was diluted with MeOH, and the solution was cooled at 0 °C. A 4 M solution of HCl in AcOEt (0.2 mL) was added to this solution, and the mixture was concentrated in vacuo. It was then recrystallized from $CHCl_3$-diethyl ether to give **12a** (0.349 mmol, 59%) as a colorless amorphous substance. $^1H$ NMR (DMSO-$d_6$) δ: 1.40–1.80 (2H, m), 2.42 (2H, m), 2.67 (1H, m), 2.72 (6H, s), 2.96–3.23 (2H, m), 3.43 (1H, m), 3.83 (3H, s), 4.06 (1H, m), 4.53 (1H, m), 4.87 (1H, m), 6.07 (1H, m), 6.79 (1H, s), 6.83 (1H, d, $J$ = 7.8 Hz), 7.00 (2H, d, $J$ = 2.9 Hz), 7.05 (2H, d, $J$ = 7.8 Hz), 7.18 (1H, dd, $J$ = 7.3, 7.8 Hz), 7.30 (1H, t, $J$ = 7.3 Hz), 7.51 (1H, d, $J$ = 7.3 Hz), 7.55 (3H, m), 9.82 (1H, s), 10.42 (1H, m). FAB MS $m/z$ $(M+H)^+$ 576. Anal. Calcd for $C_{32}H_{35}N_5O_3F_2{\cdot}HCl{\cdot}3H_2O$: C, 57.70; H, 6.35; N, 10.51; Cl, 5.32; F, 5.70. Found: C, 57.51; H, 6.30; N, 10.46; Cl, 5.33; F, 5.74.

**5.6.2. (*Z*)-*N*-[4′-({4,4-Difluoro-5-[2-(4-dimethylaminopiperidino)-2-oxoethylidene]-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl}carbonyl)phenyl]-3-methylthiophene-2-carboxamide monohydrochloride (12b).** 61% yield. $^1H$ NMR (DMSO-$d_6$) δ: 1.38–1.79 (2H, m), 2.10 (2H, m), 2.40 (3H, s), 2.42 (2H, m), 2.68 (1H, m), 2.70 (3H, s), 2.71 (3H, s), 2.98-3.23 (2H, m), 3.43 (1H, m), 4.06 (1H, m), 4.53 (1H, m), 4.87 (1H, m), 6.33 (1H, s), 6.71 (1H, d, $J$ = 7.8 Hz), 6.93 (1H, d, $J$ = 4.9 Hz), 7.10 (2H, d, $J$ = 7.8 Hz), 7.19 (1H, t, $J$ = 8.7 Hz), 7.23 (1H, t, $J$ = 7.3 Hz), 7.33 (1H, d, $J$ = 4.9 Hz), 7.40 (2H, m), 7.47 (1H, d, $J$ = 8.7 Hz), 10.07 (1H, s). FAB MS $m/z$ $(M+H)^+$ 593. Anal. Calcd for $C_{32}H_{34}N_4O_3F_2S{\cdot}HCl{\cdot}1.8\ H_2O$: C, 58.09;

H, 5.88; N, 8.47; Cl, 5.57; F, 5.74; S, 4.96. Found: C, 58.11; H, 6.12; N, 8.37; Cl, 5.57; F, 5.74; S, 4.96.

**5.6.3. (*Z*)-*N*-[4′-({4,4-Difluoro-5-[2-(4-dimethylaminopiperidino)-2-oxoethylidene]-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl}carbonyl)phenyl]-3-methylfuran-2-carboxamide monohydrochloride (12c).** 42% yield. $^1$H NMR (DMSO-$d_6$) δ: 1.42–1.82 (2H, m), 2.10 (2H, m), 2.42 (2H, m), 2.51 (6H, s), 2.67 (1H, m), 2.70 (3H, s), 2.98–3.30 (2H, m), 3.44 (1H, m), 4.06 (1H, m), 4.53 (1H, m), 4.87 (1H, m), 6.33 (1H, s), 6.38 (1H, s), 6.70 (1H, d, $J$ = 7.3 Hz), 7.08 (1H, t, $J$ = 7.3 Hz), 7.19–7.23 (3H, m), 7.35–7.40 (2H, m), 7.43 (1H, s), 8.02 (1H, s), 10.81 (1H, m). FAB MS $m/z$ $(M+H)^+$ 577. FABHRMS Calcd for $C_{32}H_{34}N_4O_4F_2$ $(M+H)^+$, 577.2626. Found: 577.2635.

**5.6.4. (*Z*)-*N*-[4′-({4,4-Difluoro-5-[2-(4-dimethylaminopiperidino)-2-oxoethylidene]-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl}carbonyl)phenyl]-2-methylfuran-3-carboxamide monohydrochloride (12d).** 61% yield. $^1$H NMR (DMSO-$d_6$) δ: 1.40–1.80 (2H, m), 2.09 (2H, br), 2.45 (2H, m), 2.50 (6H, s), 2.67 (1H, m), 2.70 (3H, s), 3.00-3.25 (2H, m), 3.37 (1H, m), 4.05 (1H, m), 4.53 (1H, m), 4.90 (1H, br), 6.78 (1H, s), 6.83 (1H, d, $J$ = 7.3 Hz), 7.06–7.10 (3H, m), 7.18 (1H, dd, $J$ = 7.3, 7.8 Hz), 7.30 (1H, dd, $J$ = 7.3, 7.8 Hz), 7.51 (1H, d, $J$ = 7.3 Hz), 7.57–7.61 (3H, m), 9.85 (1H, s). FAB MS $m/z$ $(M+H)^+$ 577. Anal. Calcd for $C_{32}H_{34}N_4O_4F_2$·HCl·0.5$H_2O$: C, 61.78; H, 5.83; N, 9.01; Cl, 5.70; F, 6.11. Found: C, 61.52; H, 5.86; N, 8.99; Cl, 5.58; F, 5.78.

**5.6.5. (*Z*)-*N*-[4′-({4,4-Difluoro-5-[2-(4-dimethylaminopiperidino)-2-oxoethylidene]-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl}carbonyl)phenyl]-5-methyloxazole-4-carboxamide (12e).** 65% yield. $^1$H NMR ($CDCl_3$) δ: 1.42–1.58 (2H, m), 1.89 (2H, m), 2.31 (6H, s), 2.43 (2H, m), 2.68 (3H, s), 2.74 (2H, m), 3.16 (2H, m), 3.97 (1H, d, $J$ = 13 Hz), 4.62 (1H, d, $J$ = 13 Hz), 5.03 (1H, m), 6.33 (1H, s), 6.70 (1H, d, $J$ = 7.3 Hz), 7.08 (1H, dd, $J$ = 7.3, 7.8 Hz), 7.15–7.30 (4H, m), 7.37 (1H, d, $J$ = 7.3 Hz), 7.48 (1H, d, $J$ = 7.3 Hz), 7.71 (1H, s), 8.72 (1H, s). FAB MS $m/z$ $(M+H)^+$ 578. Anal. Calcd for $C_{31}H_{33}N_5O_4F_2$·$H_2O$: C, 62.51; H, 5.92; N, 11.76; F, 6.38. Found: C, 62.12; H, 5.79; N, 11.80; F, 6.33.

**5.6.6. (*Z*)-*N*-(4′-{[4,4-Difluoro-5-(2-morpholino-2-oxoethylidene)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]carbonyl}phenyl)-2-methylfuran-3-carboxamide (12f).** 66% yield. $^1$H NMR (DMSO-$d_6$) δ: 2.34–2.49 (3H, m), 2.51 (3H, s), 3.10 (1H, br), 3.51–3.62 (7H, m), 4.87 (1H, br), 6.77 (1H, s), 6.82 (1H, d, $J$ = 7.3 Hz), 7.00 (1H, s), 7.07 (1H, d, $J$ = 8.7 Hz), 7.16 (1H, dd, $J$ = 7.3, 7.8 Hz), 7.28 (1H, dd, $J$ = 7.3, 7.8 Hz), 7.50 (1H, d, $J$ = 8.7 Hz), 7.57 (4H, m), 9.74 (1H, s). FAB MS $m/z$ $(M+H)^+$ 536. Anal. Calcd for $C_{29}H_{27}N_3O_5F_2$·0.2$H_2O$: C, 64.61; H, 5.12; N, 7.79; F, 7.05. Found: C, 64.55; H, 5.15; N, 7.79; F, 7.05.

**5.6.7. (*Z*)-*N*-(4′-{[4,4-Difluoro-5-(2-{[2-(4-morpholinyl)ethyl]amino}-2-oxoethylidene)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]carbonyl}phenyl)-2-methylfuran-3-carboxamide monohydrochloride (12g).** 38% yield. $^1$H NMR (DMSO-$d_6$) δ: 1.03–1.10 (2H, m), 2.40 (2H, m), 2.50 (3H, s), 3.05–3.21 (4H, m), 3.35–3.60 (6H, m), 3.81–3.98 (2H, m), 4.89 (1H, br), 6.58 (1H, s), 6.78 (1H, d, $J$ = 7.3 Hz), 7.06–7.10 (3H, m), 7.15 (1H, dd, $J$ = 7.3, 7.8 Hz), 7.28 (1H, dd, $J$ = 7.3, 7.8 Hz), 7.36 (1H, d, $J$ = 6.8 Hz), 7.55–7.58 (3H, m), 9.79 (1H, s). FAB MS $m/z$ $(M+H)^+$ 579. Anal. Calcd for $C_{31}H_{32}N_4O_5F_2$·HCl·2$H_2O$: C, 57.19; H, 5.73; N, 8.60; Cl, 5.45; F, 5.84. Found: C, 57.19; H, 5.70; N, 8.55; Cl, 5.39; F, 5.78.

**5.6.8. (*Z*)-*N*-(4′-{[4,4-Difluoro-5-(2-{[3-(4-morpholinyl)propyl]amino}-2-oxoethylidene)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]carbonyl}phenyl)-2-methylfuran-3-carboxamide (12h).** 78% yield. $^1$H NMR (DMSO-$d_6$) δ: 1.60–1.66 (2H, m), 1.89 (2H, m), 2.31 (6H, s), 2.43 (3H, m), 2.68 (3H, s), 2.74 (1H, m), 3.16 (1H, m), 3.97 (1H, d, $J$ = 13 Hz), 4.62 (1H, d, $J$ = 13 Hz), 5.03 (1H, m), 6.33 (1H, s), 6.76 (1H, d, $J$ = 7.3 Hz), 7.00 (1H, s), 7.07–7.14 (3H, m), 7.26 (1H, dd, $J$ = 7.3, 7.8 Hz), 7.34 (1H, d, $J$ = 7.8 Hz), 7.52–7.57 (2H, m), 8.33 (1H, m), 9.72 (1H, s). FAB MS $m/z$ $(M+H)^+$ 593. Anal. Calcd for $C_{32}H_{34}N_4O_5F_2$: C, 64.85; H, 5.78; N, 9.45; F, 6.41. Found: C, 64.42; H, 5.70; N, 9.41; F, 6.43.

**5.6.9. (*Z*)-*N*-(4′-{[4,4-Difluoro-5-(2-{[4-(4-morpholinyl)butyl]amino}-2-oxoethylidene)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]carbonyl}phenyl)-2-methylfuran-3-carboxamide (12i).** 72% yield. $^1$H NMR (DMSO-$d_6$) δ: 1.40 (4H, br), 2.18–2.32 (6H, m), 2.51 (3H, s), 2.52–2.67 (3H, m), 3.14 (3H, m), 3.54 (4H, m), 4.91 (1H, br), 6.45 (1H, s), 6.75 (1H, d, $J$ = 7.3 Hz), 7.01 (1H, s), 7.10–7.14 (3H, m), 7.26 (1H, dd, $J$ = 7.3, 7.8 Hz), 7.36 (1H, d, $J$ = 7.8 Hz), 7.54 (2H, m), 8.32 (1H, m), 9.72 (1H, s). FAB MS $m/z$ $(M+H)^+$ 607. Anal. Calcd for $C_{33}H_{36}N_4O_5F_2$: C, 65.33; H, 5.98; N, 9.24; F, 6.26. Found: C, 65.07; H, 6.00; N, 9.22; F, 6.28.

**5.6.10. (*Z*)-*N*-[4′-({4,4-Difluoro-5-[2-(4-morpholinopiperidino)-2-oxoethylidene]-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl}carbonyl)phenyl]-2-methylfuran-3-carboxamide monohydrochloride (12j).** 76% yield. $^1$H NMR (DMSO-$d_6$) δ: 1.38–1.92 (6H, m), 2.16–2.23 (4H, m), 2.28–2.45 (2H, m), 2.50 (3H, s), 2.68 (1H, t, $J$ = 8.8 Hz), 2.90 (4H, m), 3.17 (1H, m), 4.05 (1H, d, $J$ = 6.7 Hz), 4.52 (1H, d, $J$ = 6.7 Hz), 4.86 (1H, br), 6.44 (1H, s), 6.78 (1H, s), 7.08 (2H, m), 7.18 (1H, dd, $J$ = 7.3, 7.8 Hz), 7.30 (1H, dd, $J$ = 7.3, 7.8 Hz), 7.51 (1H, d, $J$ = 7.8 Hz), 7.60 (3H, m), 8.33 (1H, m), 9.85 (1H, s). FAB MS $m/z$ $(M+H)^+$ 619. Anal. Calcd for $C_{34}H_{36}N_4O_5F_2$·HCl·3$H_2O$: C, 57.58; H, 6.11; N, 7.90; Cl, 5.00; F, 5.36. Found: C, 57.68; H, 6.03; N, 7.87; Cl, 5.30; F, 5.37.

**5.6.11. (*Z*)-*N*-[4′-({4,4-Difluoro-5-[2-(4-isopropyl-1-piperazinyl)-2-oxoethylidene]-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl}carbonyl)phenyl]-2-methylfuran-3-carboxamide monohydrochloride (12k).** 40% yield. $^1$H NMR (DMSO-$d_6$) δ: 1.30 (6H, m), 2.42–2.48 (4H, m), 2.90–3.25 (3H, m), 3.42–3.60 (5H, m), 3.72 (1H, m), 4.13 (1H, m), 4.50 (1H, d, $J$ = 6.8 Hz), 4.85 (1H, br), 6.77 (1H, s), 6.84 (1H, d, $J$ = 7.3 Hz), 7.02 (1H, s), 7.08 (2H, d, $J$ = 7.8 Hz), 7.20 (1H, dd, $J$ = 7.3, 7.8 Hz), 7.31 (1H, dd, $J$ = 7.3, 7.8 Hz), 7.55 (3H, m), 8.31 (1H, m), 9.80 (1H, s). FAB MS $m/z$ $(M+H)^+$ 577. Anal. Calcd for $C_{32}H_{34}N_4O_4F_2$·HCl·$H_2O$: C, 60.90; H, 5.91; N, 8.88;

Cl, 5.62; F, 6.02. Found: C, 61.13; H, 5.98; N, 8.84; Cl, 5.74; F, 6.23.

**5.6.12. (*Z*)-*N*-[4′-({4,4-Difluoro-5-[2-oxoethylidene-2-(4-piperidinopiperidino)]-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl}carbonyl)phenyl]-2-methylfuran-3-carboxamide monohydrochloride (12l).** 35% yield. $^1$H NMR (DMSO-$d_6$) δ: 1.38–1.98 (8H, m), 2.16–2.25 (4H, m), 2.28–2.48 (2H, m), 2.50 (3H, s), 2.68 (1H, t, $J$ = 6.8 Hz), 2.91 (4H, m), 3.17 (1H, m), 4.05 (1H, d, $J$ = 7.6 Hz), 4.52 (1H, d, $J$ = 7.6 Hz), 4.86 (1H, br), 6.78 (1H, s), 6.84 (1H, d, $J$ = 7.3 Hz), 7.08 (2H, m), 7.18 (1H, dd, $J$ = 7.3, 7.8 Hz), 7.30 (1H, dd, $J$ = 7.3, 7.8 Hz), 7.51 (1H, d, $J$ = 7.8 Hz), 7.60 (3H, m), 8.33 (1H, m), 9.85 (1H, s). FAB MS *m*/*z* $(M+H)^+$ 617. Anal. Calcd for $C_{35}H_{38}N_4O_4F_2$·HCl·0.5$H_2O$: C, 63.49; H, 6.09; N, 8.46; F, 5.74; Cl, 5.35. Found: C, 63.30; H, 5.96; N, 8.35; F, 5.34; Cl, 5.19.

**5.6.13. (*Z*)-*N*-(4′-{[4,4-Difluoro-5-(2-oxo-2-{[3-(1-piperidinyl)propyl]amino}ethylidene)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]carbonyl}phenyl)-2-methylfuran-3-carboxamide (12m).** 87% yield. $^1$H NMR (DMSO-$d_6$) δ: 1.23 (2H, br), 1.45 (6H, br), 1.64 (2H, br), 2.35 (2H, br), 2.51 (3H, s), 2.67 (4H, br), 3.18 (4H, br), 4.89 (1H, s), 6.51 (1H, s), 6.76 (1H, d, $J$ = 7.3 Hz), 7.06–7.15 (4H, m), 7.27 (1H, dd, $J$ = 7.3, 7.8 Hz), 7.35 (1H, d, $J$ = 7.8 Hz), 7.57 (2H, d, $J$ = 7.8 Hz), 8.45 (1H, s), 9.79 (1H, s). FAB MS *m*/*z* $(M+H)^+$ 591. Anal. Calcd for $C_{33}H_{36}N_4O_4F_2$·0.2$CHCl_3$·$H_2O$: C, 63.04; H, 6.09; N, 8.86; Cl, 3.36; F, 6.01. Found: C, 62.64; H, 6.10; N, 8.94; Cl, 3.55; F, 5.95.

**5.6.14. (*Z*)-*N*-(4′-{[4,4-Difluoro-5-(2-oxo-2-{[4-(1-piperidinyl)butyl]amino}ethylidene)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]carbonyl}phenyl)-2-methylfuran-3-carboxamide monohydrochloride (12n).** 54% yield. $^1$H NMR (DMSO-$d_6$) δ: 1.37 (2H, m), 1.49 (3H, m), 1.68–1.77 (5H, m), 2.51 (3H, s), 2.82 (2H, m), 3.01 (2H, m), 3.16 (2H, m), 3.33 (3H, m), 3.38 (3H, m), 4.91 (1H, br), 6.51 (1H, s), 6.77 (1H, d, $J$ = 7.3 Hz), 7.06–7.09 (2H, m), 7.13 (1H, dd, $J$ = 7.3, 7.8 Hz), 7.27 (1H, dd, $J$ = 7.3, 7.8 Hz), 7.36 (1H, d, $J$ = 7.8 Hz), 7.55–7.58 (3H, m), 8.42 (1H, m), 9.79 (1H, s). FAB MS *m*/*z* 605. Anal. Calcd for $C_{34}H_{38}N_4O_4F_2$·HCl·2$H_2O$: C, 60.30; H, 6.40; N, 8.27; F, 5.61; Cl, 5.24. Found: C, 60.45; H, 6.21; N, 8.30; F, 5.48; Cl, 5.39.

### 5.7. Pharmacology

**5.7.1. Receptor binding assay: for the rat receptors.**[25,26] Binding assays were performed using [$^3$H]AVP on plasma membranes prepared from rat liver or kidney. Plasma membrane preparations were incubated with various concentrations of [$^3$H]AVP (0.1–3.0 nM). Radioligands (0.5 nM) were added to each membrane preparation and the mixture was incubated with various concentrations of the compounds in 250 μl of assay buffer (50 mM Tris–HCl, pH 7.5, 5 mM $MgCl_2$ and 0.1% bovine serum albumin). After incubation (60 min at 25 °C), the reaction was terminated by addition of 3 ml of ice-cooled Tris buffer (50 mM Tris–HCl, pH 7.5, 5 mM $MgCl_2$), followed immediately by filtration using glass filters. The filters were rinsed twice with Tris buffer and radioactivity retained on them was counted with a liquid scintillation counter. Specific binding was calculated as the total binding minus nonspecific binding, which was determined using 1 μM unlabeled AVP. The concentration of test compound that caused 50% inhibition ($IC_{50}$) of the specific binding of [$^3$H]AVP was determined by regression analysis of the displacement curve. Inhibitory dissociation constant ($K_i$) was calculated from the following formula: $K_i = IC_{50}/(1 + [L]/K_d)$, where [L] is the concentration of radioligand present in the tubes and $K_d$ is the dissociation constant of radioligand obtained from the Scatchard plot.

**5.7.2. Receptor binding assay: for the cloned human receptors.**[25,26] The cloned human AVP receptor subtypes were stably expressed in CHO cells and plasma membranes were prepared according to the reported protocols.

**5.7.3. $V_{1A}$ receptor antagonistic activity: in pithed rats (iv).**[25,26] Pithed rats were maintained at 37 °C by means of a thermostat-controlled heating board. For iv injection, compounds were dissolved in DMF. After the stabilization of blood pressure, compounds or vehicle was given (0.5 ml/kg iv) 5 min before the injection of AVP (30 mU/kg, iv). The dose of compound causing a 50% inhibition of the pressor response to AVP ($ID_{50}$) was calculated.

**5.7.4. $V_{1A}$ receptor antagonistic activity: in conscious rats (po).**[23] Male Wistar rats were anesthetized with pentobarbital (50 mg/kg ip). The left carotid artery and ipsilateral jugular vein were cannulated with a polyethylene tube (PE-50) for determination of blood pressure and heart rate, and for intravenous administration of AVP (30 mU/kg). The animals were allowed to recover for 2 days after operation, during which time they were housed in individual cages with free access to rat chow and water. Blood pressure was measured with a pressure transducer (AP-200T) coupled to the carotid arterial cannula and continuously recorded via a polygraph system. Heart rate was measured from blood pressure pulse waves. After stabilization of both parameters was achieved, AVP (30 mU/kg) was administered through the venous cannula. The injection of AVP was repeated at intervals of about 15 min, each injection being given as soon as blood pressure returned to a preinjection level. Responses to two consecutive doses of AVP showing approximately constant amplitudes of blood pressure elevation were averaged to be taken as a control response. Each rat was then treated orally with a single dose of the 0.5% methylcellulose aqueous solution of **12l** or the vehicle (0.5% methylcellulose aqueous solution), and any changes in blood pressure were noted.

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## References and notes


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