Preparation of Highly Potent and Selective Non-Peptide Antagonists of the Arginine Vasopressin V_{1A} Receptor by Introduction of a 2-Ethyl-1*H*-1-imidazolyl Group

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To find a new series of arginine vasopressin (AVP) V_{1A} receptor antagonists, the influence of the 2-phenyl group of 2-phenyl-4′-[(2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)carbonyl]benzanilide (7) was investigated. Replacement of the 2-phenyl group by a 2-ethyl-1*H*-imidazol-1-yl group was effective in yielding a V_{1A}-selective compound. Moreover, this imidazolyl group was introduced in the same position in YM-35471 (6), and further studies of these compounds were performed. Consequently, we found that the (*Z*)-4′-({4,4-difluoro-5-[(*N*-cyclopropylcarbamoyl)methylene]-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl}carbonyl)-2-(2-ethyl-1*H*-1-imidazol-1-yl)benzanilide (9f) exhibited highly potent affinity and selectivity, and was the most potent antagonist for the V_{1A} receptor among our compounds. The synthesis and pharmacological evaluation of these compounds are described in this paper

Key words arginine vasopressin; V_{1A} receptor selective antagonist; 2-ethyl-1*H*-1-imidazole

Arginine vasopressin (AVP) is a cyclic nonapeptide hormone secreted from the posterior pituitary gland. AVP has a variety of physiological functions, such as regulation of blood pressure, secretion of ACTH and control of water in the kidney. These physiological functions are regulated through three receptors (V_{1A}, V_{1B} and V_2). Among these receptors, the V_{1A} receptor mediates the vasoconstrictive action of AVP. The receptor is found in vascular smooth muscle, the liver, platelets, and renal mesangial cells.[1—4)]

Due to the physiological properties of AVP and the distribution of the V_{1A} receptor, abnormal secretion of AVP causes high blood pressure, cardiac disease, and kidney disease through the V_{1A} receptor.[5)] Therefore, V_{1A} receptor antagonists are expected to be important new curative drugs for these diseases. OPC-21268 (**1**) and SR49059 (**2**) have been reported as non-peptide V_{1A} receptor antagonists,[6,7)] and we have discovered and reported the 4,4-difluoro-5-methylidene-2,3,4,5-tetrahydro-1*H*-1-benzazepine derivatives as V_{1A} receptor antagonists, and introduced a 2-ethoxybenzoyl group into these derivatives (**3**, **4**) (Fig. 1).[8)]

In preceding papers,[9,10)] we reported the discovery of two AVP dual antagonists (YM087 (conivaptan), **5**; and YM-35471, **6**) which possess strong binding affinities for both V_{1A} and V_2 receptors, through optimization of the benzazepine moiety (shown in box A) of compound **7** (Fig. 2).[11)] The introduction of various groups in the 2-phenyl position (shown in box B) of compound **7** resulted in changes in selectivity between the V_{1A} and V_2 receptors. That is to say, the replacement of B with either 2-(4-NHAc)Ph or 2-(4-OMe)Ph resulted in V_{1A} receptor selectivity *versus* the V_2 receptor. On the other hand, replacement of B by 2-(3-Me)Ph, 2-(4-Et)Ph, 2-(4-NH_2)Ph or 2-(4-OH)Ph gave V_2 selectivity. For all these compounds, selectivity between the two receptors was insufficient, but we concluded that the R^2 group plays an important role in changing receptor selectivity. Therefore, we tried to convert the 2-phenyl group into other aryl groups, such as azole groups (**8a**—**g**). The most effective compound with an azole group introduced into the skeleton of (*Z*)-4′-{[(4,4-difluoro-5-carbamoylmethylene-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)carbonyl]phenyl}-benzanilide underwent further optimization of the R^3 group (**9a**—**k**), and this led to a series of compounds pos-

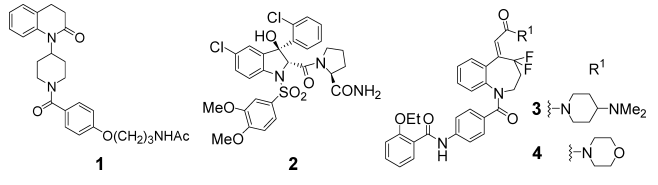

Fig. 1

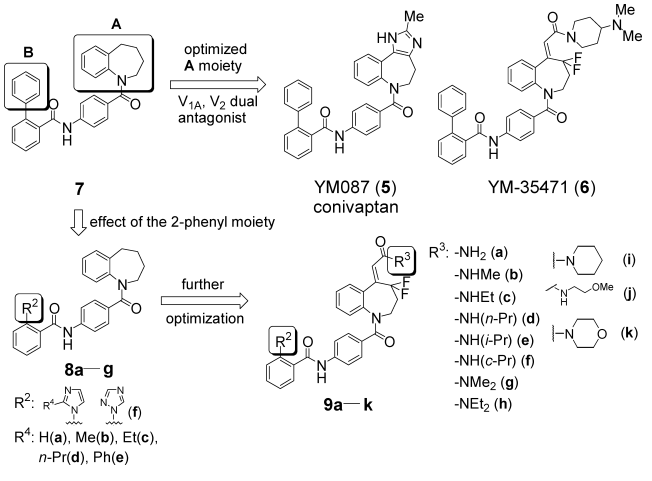

Fig. 2

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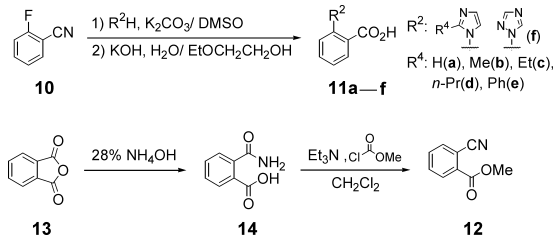


Chart 1

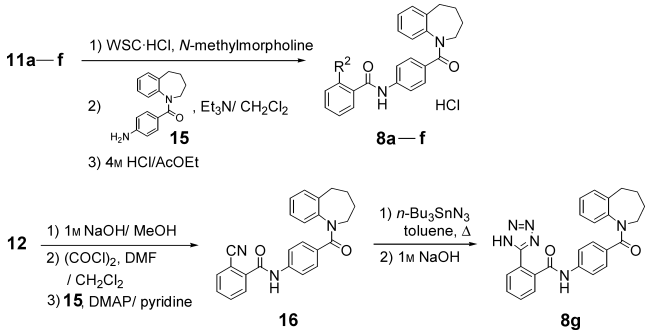


Chart 2

sessing highly potent affinity and selectivity for the V_{1A} receptor. Here, we describe the synthesis, structure–activity relationships, and pharmacological properties of these novel compounds.

Chemistry

The synthetic pathways of the compounds listed in Tables 1—3 are shown in Charts 1—3. Intermediates of 2,3,4,5-tetrahydro-1*H*-1-benzazepine derivatives (**11a**—**f**, **12**) were synthesized as outlined in Chart 1. The 2-(2-substituted-1*H*-imidazol-1-yl) or 2-(1*H*-1,2,4-triazol-1-yl) benzoic acid derivatives (**11a**—**f**) were obtained by condensation of 2-fluorobenzonitrile (**10**) and 2-substituted imidazole or a triazole,[12] followed by hydrolysis of the nitrile group under basic conditions. The methyl 2-cyanobenzoate (**12**) was synthesized as described below. The phthalic anhydride (**13**) was hydrolyzed by 28% NH_4OH to give 2-(aminocarbonyl)benzoic acid (**14**),[13] and compound **12** was obtained by treatment of **14** with methyl chloroformate.[14]

The 2,3,4,5-tetrahydro-1*H*-1-benzazepine derivatives (**8a**—**g**) were synthesized according to the route shown in Chart 2. The imidazole and triazole derivatives (**8a**—**f**) were prepared by condensation of 1-(4-aminobenzoyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepine (**15**)[11] and **11a**—**f** in the presence of 1-ethyl-3-(dimethylaminopropyl) carbodiimide hydrochloride (WSC·HCl). Compound **12** was hydrolyzed with 1 M NaOH to give the corresponding carboxylic acid derivative, followed by the addition of oxalyl chloride to give the acyl chloride derivative. This acyl chloride was condensed with **15** to give the 2-cyanobenzanilide derivative **16**. The tetrazole derivative (**8g**) was synthesized by treating **16** with *n*-Bu_3SnN_3.[15,16]

The 4,4-difluoro-5-methylidene-2,3,4,5-tetrahydro-1*H*-1-benzazepine derivatives (**9a**—**k**) were prepared according to the methods shown in Chart 3. The methyl ester derivative **18** was obtained by acylation of **17**[10] with the acyl chloride derivative of **11c**. Hydrolysis of the methyl ester in **18** with

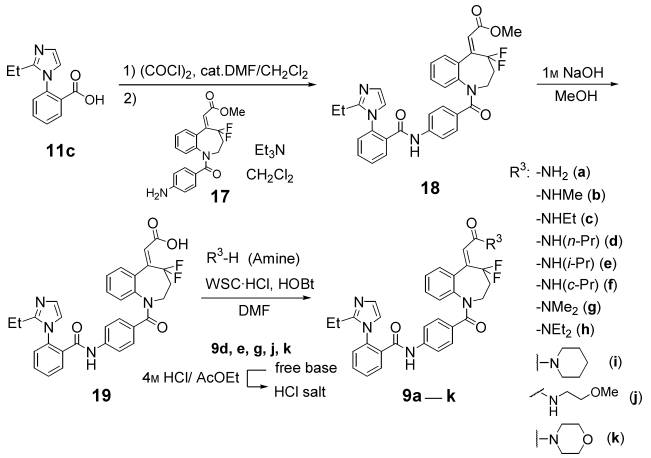


Chart 3

1 M NaOH afforded the acetic acid derivative **19**. The target compounds (**9a**—**k**) were synthesized by condensation of **19** and various amines in the presence of WSC·HCl and 1-hydroxybenzotriazole (HOBt).

Results and Discussion

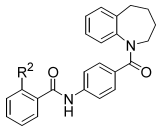
Binding Affinities Methods for determining the *in vitro* AVP receptor binding affinities have been described in a previous paper.[8] The results of binding assay of the compounds are shown in Tables 1—3. Initially, we investigated the role of the R^2 position in V_{1A} selectivity in 2,3,4,5-tetrahydro-1*H*-1-benzazepine derivatives, as shown in Table 1. When the 1*H*-imidazol-1-yl group (**8a**) was introduced at the R^2 position, selectivity for the V_{1A} receptor *versus* the V_2 receptor was greater than that of **7**. Additionally, the 1*H*-1,2,4-triazol-1-yl (**8f**) and 1*H*-tetrazol-1-yl (**8g**) derivatives showed slight V_{1A} selectivity, but the V_{1A} binding affinity of these derivatives (**8f**, **g**) decreased compared to **7**. It was concluded that the nitrogen atom of the azole group contributed to the increase in V_{1A} receptor selectivity.

Among compounds **8a**, **8f** and **8g**, the imidazole derivative (**8a**) tended to possess higher V_{1A} binding affinity and selectivity than **8f** or **8g**, and the imidazolyl moiety was therefore studied further. The methyl (**8b**) and ethyl (**8c**) derivatives at the 2-position of imidazole (R^4) exhibited highly potent binding affinity and selectivity for the V_{1A} receptor, but the introduction of a bulky substituent such as an *n*-propyl or phenyl group (**8d**, **e**) decreased the affinity and selectivity. Consequently, the introduction of a 2-ethyl-1*H*-imidazol-1-yl group was effective in increasing V_{1A} receptor selectivity *versus* the V_2 receptor, while maintaining the V_{1A} binding affinity. These observations suggested that V_{1A} binding affinity and selectivity were influenced by both the electronic effect of the azole group and the steric effect of the substituent at the R^4 position.

Based on these results, we tried to convert the 2-phenyl group of compound **6** (YM-35471 skeleton) into a 2-ethyl-1*H*-imidazol-1-yl group, and further modifications of various amide groups at the R^3 position were performed.

Because the YM-35471 skeleton possesses high binding affinities for the V_{1A} and V_2 receptors, we thought that introduction of a 2-ethyl-1*H*-imidazol-1-yl group might give compounds with both highly potent binding affinity and selectiv-

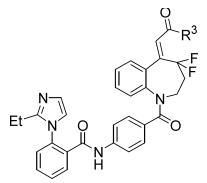
Table 1. Receptor-Binding Affinities of 2,3,4,5-Tetrahydro-1*H*-1-benzazepine Derivatives



No.	R^2	R^4	Binding affinity (pK_i)		V_{1A}/V_2 [c]
			V_{1A} [a]	V_2 [b]	
7 [d]	Ph	—	7.85	8.12	0.54
8a		H	7.33	6.43	8
8b		Me	8.20	6.79	26
8c		Et	8.58	7.21	23
8d		*n*-Pr	7.40	6.97	3
8e		Ph	6.31	5.71	4
8f		—	7.16	6.42	5
8g		—	6.63	6.22	3

a) pK_i of [^{3}H]-vasopressin binding to rat liver membranes. *b*) pK_i of [^{3}H]-vasopressin binding to rat kidney membranes. *c*) V_{1A}/V_2 shows the selectivity for binding with the V_{1A} receptor *versus* the V_2 receptor. *d*) See ref. 8.

Table 2. Receptor-Binding Affinities of 4,4-Difluoro-5-methylidene-2,3,4,5-tetrahydro-1*H*-1-benzazepine Derivatives



No.	R^3	Binding affinity (pK_i)		V_{1A}/V_2 [c]
		V_{1A} [a]	V_2 [b]	
6 [d]	—	10.10	9.58	3
8c	—	8.58	7.21	23
9a	$-NH_2$	8.70	6.35	224
9b	–NHMe	9.01	6.68	214
9c	–NHEt	9.01	6.92	123
9d	–NH(*n*-Pr)	8.72	6.38	219
9e	–NH(*i*-Pr)	8.85	6.42	269
9f	–NH(*c*-Pr)	9.47	6.81	457
9g	$-NMe_2$	8.84	6.65	155
9h	$-NEt_2$	8.86	7.41	28
9i		8.79	7.06	54
9j		8.92	7.06	72
9k		9.27	6.96	204

a—*c*) See footnotes in Table 1. *d*) Compound **6** has a phenyl group at the same position as the 2-ethyl-1*H*-imidazol-1-yl group.

Table 3. Binding Affinities of Compounds **9f** and **6** for Cloned Human V_{1A} (hV_{1A}) and V_2 (hV_2) Receptors and AVP-Antagonist Activities

No.	Binding affinity (pK_i)		V_{1A}/V_2 [c]
	hV_{1A} [a]	hV_2 [b]	
9f	9.00	6.85	140
6	9.21	8.92	2

a, *b*) See ref. 8. *c*) See footnote in Table 1.

ity for the V_{1A} receptor. The binding affinities of 4,4-difluoro-5-methylidene-2,3,4,5-tetrahydro-1*H*-1-benzazepine derivatives are shown in Table 2. All these derivatives (**9a**—**k**) showed an increase in V_{1A} receptor selectivity *versus* the V_2 receptor, compared to **6** and **8c**, and exhibited more potent binding affinity for the V_{1A} receptor, compared to **8c**. The alkyl-substituted derivatives (**9b**—**i**) possessed highly potent binding affinity compared with the carbamoyl derivative **9a**, but the introduction of a bulky substituent group, such as in compounds **9h** and **9i**, was found to decrease selectivity for the V_{1A} receptor. The cyclopropyl-substituted derivative (**9f**) exhibited the most potent affinity among these derivatives and showed a 457-fold selectivity for the V_{1A} *versus* the V_2 receptor. In the derivatives containing oxygen atoms (**9j**, **k**), the V_{1A} selectivity of **9j** was insufficient, but compound **9k** showed a more potent affinity for the V_{1A} receptor, compared with corresponding hydrocarbon derivative (**9i**). Therefore, the influence of the oxygen atom in V_{1A} selectivity was unclear. These results suggested that V_{1A} binding affinity and selectivity are influenced by a steric effect at the R^3 position, making substitution with a cyclopropyl group suitable for obtaining the desired compound.

Subsequently, we investigated the binding affinities of compound **9f** for cloned human V_{1A} (hV_{1A}) and V_2 (hV_2) receptors (Table 3).[8] Compound **9f** exhibited potent binding affinity for the V_{1A} receptor and 140-fold selectivity for the V_{1A} *versus* the V_2 receptor. Additionally, **9f** showed 70-fold V_{1A} selectivity compared to **6**. Therefore, conversion of the 2-phenyl group into a 2-ethyl-1*H*-imidazol-1-yl group also contributed to increased V_{1A} selectivity in cloned human AVP receptors.

Antagonist Activity The V_{1A} receptor antagonist activity was determined by measuring inhibition of the AVP-induced diastolic blood pressure (DBP) response in pithed rats after intravenous (i.v.) administration. The dose of the compound causing a 50% inhibition of the pressor response to AVP (ID_{50}) was calculated. The experimental method used to determine AVP antagonist activity has been described in a previous paper.[8]

Compound **9f** was selected and the above *in vivo* experiment was performed. Results showed that **9f** exhibited potent antagonist activity (ID_{50}: 0.0010 mg/kg i.v.) for the V_{1A} receptor. Furthermore, the antagonist activity of **9f** was more effective than that of **6** (ID_{50}: 0.0027 mg/kg i.v.). Therefore, introduction of a 2-ethyl-1*H*-imidazol-1-yl group at the R^2 position and a cyclopropylamino group at the R^4 position provided the most potent V_{1A} receptor antagonist activity.

Conclusion

In this paper, we have described the synthesis of 2-substituted 4′-[(2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)carbonyl] benzanilide derivatives and (*Z*)-2-substituted 4′-[(4,4-difluoro-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)carbonyl]benzanilide derivatives, and evaluated their AVP receptor binding affinities and antagonist activities. It was found that the introduction of a 2-ethyl-1*H*-imidazol-1-yl group at the 2-position increased V_{1A} selectivity *versus* the V_2 receptor. In particular, (*Z*)-4′-({4,4-difluoro-5-[(*N*-cyclopropylcarbamoyl)-methylene]-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl}carbonyl)-2-(2-ethyl-1*H*-1-imidazol-1-yl)benzanilide (**9f**) exhibited potent binding affinity for the V_{1A} receptor and high

Table 4. Physical and Spectral Data for the 2-Substituted Benzoic Acid Derivatives

No.	R^2	R^4	Yield (%)	^{1}H-NMR (DMSO-d_6) δ	EI-MS m/z (M^+)
11a		H	64	7.65—7.89 (4H, m), 7.95—8.01 (1H, m), 8.08—8.19 (1H, m), 9.05 (1H, m)	188
11b		Me	74	2.19 (3H, s), 7.52—7.93 (4H, m), 7.95—8.11 (1H, m), 8.21—8.25 (1H, m)	202
11c		Et	60	1.13 (3H, t, J=7 Hz), 3.55 (2H, q, J=7 Hz), 7.61—7.90 (4H, m), 7.99—8.07 (1H, m), 8.10—8.19 (1H, m)	216
11d		*n*-Pr	52	0.76 (3H, t, J=7 Hz), 2.03 (2H, m), 2.47 (2H, m), 7.34—7.80 (4H, m), 7.91—8.03 (1H, m), 8.09—8.21 (1H, m)	230
11e		Ph	19	7.14—7.45 (6H, m), 7.51—7.70 (3H, m), 7.89—8.01 (2H, m)	264
11f		—	38	7.47—7.72 (4H, m), 7.85—8.05 (1H, m), 8.64 (1H, m)	189

antagonist activity following i.v. administration. Further efforts to develop AVP antagonists are ongoing.

Experimental

^{1}H- and ^{13}C-NMR spectra were obtained on a JNM-400 spectrometer. 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; q, quartet; m, multiplet; br, broad peak. Mass spectra were obtained using a JEOL JMS-DX300 spectrometer. Elemental analysis was performed with a Yanaco MT-5. Melting points were determined on a Yanaco MP-500D micro melting point apparatus without correction. Column chromatography on silica gel was performed using Merck KGaA Silica gel 60 (0.040—0.063 mm).

General Procedure for Synthesis of 2-Substituted Benzoic Acid Derivatives (11a—f)[12] A mixture of 2-fluorocyanobenzene (**10**, 5.00 g, 41.3 mmol), imidazole derivatives or 1*H*-1,2,4-triazole (41.3 mmol) and K_2CO_3 (6.39 g, 45.4 mmol) in dimethyl sulfoxide (DMSO, 25 ml) was stirred at 100 °C for 3 h. After cooling, the reaction mixture was poured into H_2O (50 ml) and the product was precipitated readily and separated out. The precipitate was washed with H_2O (50 ml×2) and dried to give 2-substituted cyanobenzene derivatives. Then, these derivatives were hydrolyzed with KOH (14.5 g, 258 mmol), H_2O (3.0 ml), and 2-ethoxyethanol (30 ml). After refluxing for 3 h, the reaction mixture was diluted with H_2O and acidified with 12 M HCl (20 ml) under cooling at 0 °C. The mixture was extracted with $CHCl_3$ (50 ml×2). The organic layer was concentrated *in vacuo* and the residual solvent was separated as the ethanol (EtOH) azeotrope. The residue was diluted with brine and extracted with $CHCl_3$ (50 ml×2). The organic extract was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The 2-substituted benzoic acid derivatives (**11a**—**f**) were obtained as a colorless crystal by recrystallization from 2-propanol-methanol (MeOH). All physical and spectral data for the 2-substituted benzoic acid derivatives are shown in Table 4.

Phthalamic Acid (14)[13] A suspension of phthalic anhydride (**13**, 10.0 g, 67.5 mmol) in 28% NH_4OH (50 ml) was stirred at 70 °C for 10 min, and the reagent was dissolved. After cooling to 0 °C, the product precipitated readily and was separated out. To the filtrate, tetrahydrofuran (THF, 50 ml) was added and the precipitate was obtained again. The combined precipitates were dissolved in H_2O (25 ml) and a reprecipitation was performed with the addition of 12 M HCl (10 ml, dropwise) while cooling. The precipitate was filtered and dried. The compound **14** (4.69 g, 28.4 mmol, 42%) was obtained as a colorless crystal. ^{1}H-NMR (DMSO-d_6) δ: 7.29 (1H, br), 7.35—7.58 (3H, m), 7.65—7.76 (2H, m), 12.8 (1H, br). FAB-MS m/z: 166 (M^++1).

Methyl 2-Cyanobenzoate (12)[14] To a stirred suspension of compound **14** (3.52 g, 21.3 mmol) in CH_2Cl_2 (50 ml) at 0 °C were added triethylamine (Et_3N; 6.23 ml, 44.7 mmol) and methyl chloroformate (3.62 ml, 46.8 mmol). After stirring at room temperature for 8 h, the reaction mixture was extracted with $CHCl_3$, washed with H_2O, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The product was washed with hexane and dried. The title compound **12** (3.34 g, 20.7 mmol, 97% yield) was obtained as a colorless crystal. ^{1}H-NMR ($CDCl_3$) δ: 3.98 (3H, s), 7.62—7.88 (3H, m), 8.06—8.21 (1H, m). GC-MS m/z: 161 (M^+).

2-(1*H*-Imidazol-1-yl)-4′-[(2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)-carbonyl]benzanilide Monohydrochloride (8a) To a cooled mixture of **11a** (170 mg, 0.90 mmol) in CH_2Cl_2 (3 ml) and *N*-methylmorpholine (0.12 ml) was added 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride (WSC·HCl; 190 mg, 0.90 mmol). After the mixture was stirred for 1 h, a solution of **15**[11] (200 mg, 0.751 mmol) in CH_2Cl_2 (3 ml) was added. The whole mixture was stirred at room temperature overnight. To the mixture was added a saturated aqueous solution of $NaHCO_3$, and it was extracted with $CHCl_3$. The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent, $CHCl_3$: MeOH=19 : 1), yielding 286 mg (0.655 mmol, 87% yield) of **8a** as a free amine. The resulting amine (236 mg, 0.602 mmol) was diluted with ethyl acetate (AcOEt; 10 ml), and the solution was cooled at 0 °C. To this solution, 4 M solution of HCl in AcOEt (4 M HCl/AcOEt; 10 ml) was added. The mixture was subsequently concentrated *in vacuo* and recrystallized from MeOH–diethyl ether (Et_2O) to give 200 mg (0.422 mmol, 56% from **11a**) of **8a** as a colorless amorphous substance. ^{1}H-NMR (DMSO-d_6) δ: 1.40 (1H, m), 1.84 (2H, m), 1.99 (1H, m), 2.65 (1H, m), 2.88 (1H, m), 2.94 (1H, m), 4.82 (1H, m), 6.69 (1H, d, J=7 Hz), 6.96 (1H, m), 7.10 (3H, m), 7.29 (1H, d, J=7 Hz), 7.41 (2H, d, J=7 Hz), 7.65 (4H, m), 7.88 (2H, m), 9.45 (1H, s), 10.72 (1H, s). FAB-MS m/z: 465 (M^++1).

The compounds **8b**—**f** were prepared from **15** and **11b**—**f** in the same manner as described in the synthesis of **8a**.

2-(2-Methyl-1*H*-imidazol-1-yl)-4′-[(2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)carbonyl]benzanilide Monohydrochloride (8b) Colorless amorphous substance. Yield: 71%. ^{1}H-NMR (DMSO-d_6) δ: 1.55 (1H, m), 2.05 (3H, m), 2.19 (3H, s), 2.76 (1H, m), 2.87 (1H, m), 3.05 (1H, m), 5.02 (1H, m), 6.58 (1H, d, J=7 Hz), 6.73 (1H, s), 6.90 (1H, m), 7.12 (6H, m), 7.32—7.42 (3H, m), 7.65 (2H, m), 8.05 (1H, m). FAB-MS m/z: 451 (M^++1).

2-(2-Ethyl-1*H*-imidazol-1-yl)-4′-[(2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)carbonyl]benzanilide Monohydrochloride (8c) Colorless amorphous substance. Yield: 30%. ^{1}H-NMR (DMSO-d_6) δ: 1.13 (3H, t, J=7 Hz), 1.57 (1H, m), 1.99 (2H, m), 2.04 (1H, m), 2.48 (2H, q, J=7 Hz), 2.74 (1H, m), 2.87 (1H, m), 3.00 (1H, m), 4.99 (1H, m), 6.61 (1H, d, J=7 Hz), 6.74 (1H, s), 6.90 (1H, m), 7.07 (6H, m), 7.22—7.32 (3H, m), 7.63 (2H, m), 8.09 (1H, d, J=7 Hz). FAB-MS m/z: 465 (M^++1).

2-(2-Propyl-1*H*-imidazol-1-yl)-4′-[(2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)carbonyl]benzanilide Monohydrochloride (8d) Colorless amorphous substance. Yield: 72%. ^{1}H-NMR (DMSO-d_6) δ: 0.75 (3H, t, J=7 Hz), 1.62 (4H, m), 2.04 (2H, m), 2.48 (2H, m), 2.74 (1H, m), 2.83 (1H, m), 2.98 (1H, m), 4.99 (1H, m), 6.58 (1H, d, J=7 Hz), 6.78 (1H, s), 6.90 (1H, m), 7.10 (6H, m), 7.15—7.35 (3H, m), 7.70 (2H, m), 8.11 (1H, d, J=7 Hz). FAB-MS m/z: 479 (M^++1).

2-(2-Phenyl-1*H*-imidazol-1-yl)-4′-(2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)carbonyl]benzanilide Monohydrochloride (8e) Colorless amorphous substance. Yield: 68%. ^{1}H-NMR (DMSO-d_6) δ: 1.82 (3H, m), 2.91 (4H, m), 4.82 (1H, m), 6.72 (2H, m), 7.12 (4H, m), 7.39 (8H, m), 7.72 (3H, m), 7.90 (2H, d, J=7 Hz), 10.39 (1H, s). FAB-MS m/z: 513 (M^++1).

2-(1*H*-1,2,4-Triazol-1-yl)-4′-[(2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)carbonyl]benzanilide Monohydrochloride (8f) Colorless amorphous substance. Yield: 33%. ^{1}H-NMR (DMSO-d_6) δ: 1.93 (3H, m), 2.90 (4H, m), 5.00 (1H, m), 6.67 (1H, d, J=7 Hz), 6.80—7.10 (3H, m), 7.20 (5H, m),

7.41—7.75 (3H, m), 8.07 (1H, s), 8.16 (1H, br), 8.36 (1H, s). FAB-MS *m/z*: 438 ($M^+ + 1$).

4′-[(2,3,4,5-Tetrahydro-1*H*-1-benzazepin-1-yl)carbonyl]-2-cyanobenzanilide (16) The mixture of compound **12** (3.29 g, 20.4 mmol), MeOH (60 ml) and 1 M NaOH (22 ml) were stirred at room temperature for 8 h, and then concentrated *in vacuo*. The residue was diluted with H_2O and $CHCl_3$, and then acidified with 1 M HCl (22 ml) under cooling. The resulting precipitate was collected, washed with H_2O and hexane, and dried *in vacuo*. The corresponding benzoic acid derivative (2.21 g, 15.0 mmol, 74%) was obtained as a colorless crystal. The benzoic acid derivatives (663 mg, 4.51 mmol) and a drop of *N*,*N*-dimethylformamide (DMF) in CH_2Cl_2 (30 ml) was added oxalyl chloride (0.59 ml, 6.76 mmol). The mixture was stirred at room temperature for 2 h and concentrated *in vacuo* to give colorless oil. To an ice-cooled mixture of **15**[11] (1.00 g, 3.76 mmol), pyridine (20 ml) and a catalytic amount of 4-dimethylaminopyridine (DMAP) was added a solution of above colorless oil in CH_2Cl_2 (20 ml). The mixture was stirred at room temperature for 8 h, and then concentrated *in vacuo*. The residue was diluted with $CHCl_3$, and the organic layer was washed with 1 M NaOH, 1 M HCl, and brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (eluent, $CHCl_3$/AcOEt=20/1) and recrystallized from $CHCl_3$–Et_2O to give 932 mg of **16** (2.36 mmol, 63%) as a yellow crystal. ^{1}H-NMR ($CDCl_3$) δ: 1.80—2.35 (3H, m), 2.70—3.15 (4H, m), 5.05 (1H, m), 6.70 (1H, d, J=7 Hz), 6.95—7.50 (7H, m), 7.70—8.15 (4H, m). FAB-MS *m/z*: 396 ($M^+ + 1$).

4′-[(2,3,4,5-Tetrahydro-1*H*-1-benzazepin-1-yl)carbonyl]-2-(1*H*-tetrazol-5-yl)benzanilide (8g)[15,16] A mixture of compound **16** (932 mg, 2.36 mmol) and azidotributyltin (1.17 g, 3.54 mmol) in toluene (20 ml) was refluxed for 24 h. An additional amount of azidotributyltin (2.73 g, 8.25 mmol) was added and the mixture was refluxed for 48 h. After cooling at room temperature, to the stirred mixture was added Et_2O (20 ml) and 1 M NaOH (20 ml). After 30 min, the reaction mixture was extracted with 1 M NaOH (20 ml×2), and the combined extracts were acidified with 12 M HCl (30 ml) under cooling. The solution was extracted with $CHCl_3$ and the organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (eluent, $CHCl_3$/MeOH=30/1) and recrystallized from a mixture of $CHCl_3$ and Et_2O to give 351 mg (0.80 mmol, 34%) of **8g** as a yellow amorphous substance. ^{1}H-NMR (DMSO-d_6) δ: 1.60—2.15 (3H, m), 2.53—3.17 (4H, m), 4.85 (1H, m), 6.75 (1H, m), 6.97—7.25 (4H, m), 7.33—7.50 (3H, m), 7.70—7.82 (4H, m), 10.50 (1H, s). FAB-MS *m/z*: 439 ($M^+ + 1$).

Methyl (*Z*)-(1-{4-[2-(2-ethyl-1*H*-imidazol-1-yl)benzoylamino]benzoyl}-4,4-difluoro-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-ylidene)acetate (18) To an ice-cooled mixture of 2-(2-ethyl-1*H*-imidazol-1-yl)benzoic acid (**11c**, 3.00 g, 13.9 mmol) and a drop of DMF in CH_2Cl_2 (60 ml) was added oxalyl chloride (1.82 ml, 20.9 mmol). The mixture was stirred at room temperature for 3 h, diluted with $CHCl_3$, and concentrated *in vacuo* to give a colorless powder. The colorless powder (acyl chloride derivatives) was used after the reaction without further purification. To an ice-cooled mixture of methyl (*Z*)-[1-(4-aminobenzoyl)-4,4-difluoro-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-ylidene]acetate (**17**)[10] (4.31 g, 11.6 mmol) and Et_3N (1.94 ml) in CH_2Cl_2 (40 ml) was added a solution of this colorless powder in CH_2Cl_2 (30 ml). The mixture was stirred at room temperature for 8 h, and then concentrated *in vacuo*. The residue was diluted with chloroform and the organic layer was washed with saturated aqueous solution of Na_2CO_3, 1 M HCl and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The crude product was chromatographed on a silica gel column using $CHCl_3$–MeOH (95 : 5), and recrystallized from MeOH–toluene to give 4.96 g of **18** (8.70 mmol, 75% yield) as a colorless amorphous substance. ^{1}H-NMR (DMSO-d_6) δ: 1.04 (3H, t, J=7 Hz), 2.39 (2H, q, J=7 Hz), 2.50 (1H, m), 3.11 (1H, br), 3.32 (1H, s), 3.74 (3H, s), 4.86 (1H, br), 6.77 (1H, d, J=7 Hz), 6.80 (2H, d, J=7 Hz), 7.01 (2H, d, J=7 Hz), 7.06 (1H, s), 7.20 (1H, t, J=8 Hz), 7.29 (1H, t, J=8 Hz), 7.37—7.44 (4H, m), 7.60—7.70 (3H, m), 10.40 (1H, s). FAB-MS *m/z*: 571 ($M^+ + 1$).

(*Z*)-(1-{4-[2-(2-Ethyl-1*H*-imidazol-1-yl)benzoylamino]benzoyl}-4,4-difluoro-2,3,4,5-tetrahydro-1*H*-1-benzazepin-5-ylidene)acetic Acid (19) The mixture of compound **18** (4.50 g, 7.89 mmol) in MeOH (30 ml) and 1 M NaOH (12 ml) was stirred at room temperature for 8 h, and then concentrated *in vacuo*. The residue was diluted with H_2O and $CHCl_3$, and then acidified with 1 M HCl (20 ml) under cooling. The mixture was extracted with $CHCl_3$ and the organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was recrystallized from 2-propanol to give 4.50 g of **19** (quant.) as a colorless amorphous substance. ^{1}H-NMR (DMSO-d_6) δ: 1.04 (3H, t, J=7 Hz), 2.40 (2H, q, J=7 Hz), 2.50 (1H, m), 3.08 (1H, br), 3.17 (1H, s), 4.86 (1H, br), 6.60 (1H, s), 6.80 (1H, s), 7.01 (2H, d, J=7 Hz), 7.08 (1H, s), 7.17 (1H, t, J=8 Hz), 7.29 (1H, t, J=8 Hz), 7.35—7.45 (4H, m), 7.60—7.71 (3H, m), 10.41 (1H, s). FAB-MS *m/z*: 557 ($M^+ + 1$).

(*Z*)-4′-[(5-Carbamoylmethylene-4,4-difluoro-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)carbonyl]-2-(2-ethyl-1*H*-imidazol-1-yl)benzanilide (9a) A mixture of compound **19** (1.0 g, 1.80 mmol), HOBt (292 mg, 2.16 mmol) and WSC·HCl (414 mg, 2.16 mmol) in DMF (20 ml) was stirred at room temperature for 1 h. After being cooled at 0 °C, 28% NH_4OH (3 ml) was added, and the mixture was stirred at room temperature for 8 h. To the mixture was added saturated aqueous solution of $NaHCO_3$ and extracted with AcOEt. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on a silica gel column using $CHCl_3$–MeOH (95 : 5) as the eluent, then recrystallized from 2-propanol to give 583 mg (1.05 mmol, 58%) of **9a** as a colorless powder. mp 292—293 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.04 (3H, t, J=8 Hz), 2.39 (2H, q, J=8 Hz), 2.50 (1H, s), 2.65 (1H, br), 3.32 (1H, s), 4.87 (1H, br), 6.48 (1H, s), 6.75 (1H, d, J=7 Hz), 6.79 (1H, s), 7.06 (3H, m), 7.13 (1H, t, J=8 Hz), 7.25—7.37 (5H, m), 7.43 (1H, d, J=7 Hz), 7.59—7.77 (3H, m), 7.95 (1H, s), 10.39 (1H, s). FAB-MS *m/z*: 556 ($M^+ + 1$). *Anal.* Calcd for $C_{31}H_{27}N_5O_3F_2 \cdot 0.1H_2O$: C, 66.78; H, 4.24; N, 12.56; F, 6.81. Found: C, 66.35; H, 4.97; N, 12.56; F, 6.84.

Compounds **9b**—**k** were synthesized in the same manner.

(*Z*)-4′-({4,4-Difluoro-5-[(*N*-methylcarbamoyl)methylene]-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl}carbonyl)-2-(2-ethyl-1*H*-1-imidazol-1-yl)benzanilide (9b) Colorless powder. Yield: 37%. mp 280—281 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.04 (3H, t, J=8 Hz), 2.37 (1H, br), 2.40 (2H, q, J=8 Hz), 2.50 (3H, d, J=7 Hz), 3.04 (1H, br), 3.33 (1H, s), 4.88 (1H, br), 6.50 (1H, s), 6.70 (1H, d, J=7 Hz), 6.79 (1H, s), 7.06 (3H, m), 7.14 (1H, t, J=8 Hz), 7.25—7.37 (4H, m), 7.42 (1H, d, J=7 Hz), 7.59—7.70 (3H, m), 8.21 (1H, m), 10.38 (1H, s). FAB-MS *m/z*: 570 ($M^+ + 1$). *Anal.* Calcd for $C_{32}H_{29}N_5O_3F_2$: C, 67.48; H, 5.13; N, 12.30; F, 6.67. Found: C, 67.19; H, 5.30; N, 12.32; F, 6.61.

(*Z*)-4′-({4,4-Difluoro-5-[(*N*-ethylcarbamoyl)methylene]-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl}carbonyl)-2-(2-ethyl-1*H*-1-imidazol-1-yl)benzanilide (9c) Colorless powder. Yield: 63%. mp 272—274 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.04 (3H, t, J=8 Hz), 1.06 (3H, t, J=8 Hz), 2.40 (4H, q, J=8 Hz), 3.15 (2H, br), 3.32 (1H, s), 4.88 (1H, br), 6.49 (1H, s), 6.74 (1H, d, J=7 Hz), 6.79 (1H, s), 7.03—7.07 (2H, m), 7.13 (1H, t, J=8 Hz), 7.27 (1H, t, J=8 Hz), 7.34 (4H, m), 7.43 (1H, d, J=7 Hz), 7.59—7.70 (3H, m), 8.27 (1H, t, J=8 Hz), 10.38 (1H, s). FAB-MS *m/z*: 584 ($M^+ + 1$). *Anal.* Calcd for $C_{33}H_{31}N_5O_3F_2$: C, 67.91; H, 5.35; N, 12.00; F, 6.51. Found: C, 67.64; H, 5.45; N, 11.79; F, 6.46.

(*Z*)-4′-({4,4-Difluoro-5-[(*N*-1-propylcarbamoyl)methylene]-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl}carbonyl)-2-(2-ethyl-1*H*-1-imidazol-1-yl)benzanilide Monohydrochloride (9d) The free amine of **9d** was dissolved in 2-propanol (6 ml), and to this ice-cooled solution was added 4 M HCl/AcOEt (0.2 ml). The resulting precipitate was filtered and dried to give **9d** (70%) as a colorless powder. mp 252—254 °C. ^{1}H-NMR (DMSO-d_6) δ: 0.88 (3H, m), 1.14 (3H, m), 1.45 (2H, m), 2.34 (1H, br), 2.71 (3H, br), 3.07 (2H, br), 3.43 (1H, br), 4.88 (1H, br), 6.52 (1H, s), 6.75 (1H, d, J=7 Hz), 7.06—7.15 (3H, m), 7.26 (1H, t, J=8 Hz), 7.36 (1H, d, J=7 Hz), 7.43 (2H, d, J=7 Hz), 7.59—7.96 (6H, m), 8.32 (1H, m), 10.81 (1H, s). FAB-MS *m/z*: 598 ($M^+ + 1$). *Anal.* Calcd for $C_{34}H_{33}N_5O_3F_2 \cdot HCl \cdot 0.5H_2O$: C, 63.50; H, 5.49; N, 10.89; F, 5.91; Cl, 5.51. Found: C, 63.30; H, 5.33; N, 10.81; F, 5.60; Cl, 5.54.

(*Z*)-4′-({4,4-Difluoro-5-[(*N*-2-propylcarbamoyl)methylene]-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl}carbonyl)-2-(2-ethyl-1*H*-1-imidazol-1-yl)benzanilide Monohydrochloride (9e) The free amine of **9e** was dissolved in 2-propanol (10 ml), and to this ice-cooled solution was added 4 M HCl/AcOEt (0.2 ml). After removing the volatiles, the residue was recrystallized from CH_3CN and dried to give **9e** (89%) as a colorless powder. mp 182—184 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.10 (3H, s), 1.12 (3H, s), 1.15 (3H, t, J=8 Hz), 2.07 (2H, s), 2.70 (2H, br), 3.07 (1H, br), 3.94 (1H, m), 4.88 (1H, br), 6.50 (1H, s), 6.75 (1H, d, J=7 Hz), 7.06 (2H, d, J=7 Hz), 7.13 (2H, t, J=8 Hz), 7.27 (1H, t, J=8 Hz), 7.34 (1H, d, J=7 Hz), 7.44 (2H, d, J=7 Hz), 7.70—7.81 (4H, m), 7.93 (1H, m), 8.15 (1H, d, J=7 Hz), 10.80 (1H, s). FAB-MS *m/z*: 598 ($M^+ + 1$). *Anal.* Calcd for $C_{34}H_{33}N_5O_3F_2 \cdot HCl \cdot 2.5H_2O$: C, 60.13; H, 5.79; N, 10.31; F, 5.59; Cl, 5.22. Found: C, 59.66; H, 5.31; N, 10.20; F, 5.54; Cl, 5.19.

(*Z*)-4′-({4,4-Difluoro-5-[(*N*-cyclopropylcarbamoyl)methylene]-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl}carbonyl)-2-(2-ethyl-1*H*-1-imidazol-1-yl)benzanilide (9f) Colorless powder. Yield: 27%. mp 265—267 °C. ^{1}H-NMR (DMSO-d_6) δ: 0.45 (2H, m), 0.66 (2H, m), 1.04 (3H, t, J=8 Hz), 2.41 (2H, q, J=8 Hz), 2.35 (1H, br), 2.50 (1H, s), 3.04 (1H, br), 3.32 (1H, s), 4.87

(1H, br), 6.48 (1H, s), 6.73 (1H, d, J=7 Hz), 6.79 (1H, s), 7.03—7.07 (3H, m), 7.14 (1H, t, J=8 Hz), 7.24—7.40 (4H, m), 7.44 (1H, d, J=7 Hz), 7.60—7.70 (3H, m), 8.34 (1H, d, J=7 Hz), 10.41 (1H, s). ^{13}C-NMR (DMSO-d_6) δ: 5.40 (s), 11.9 (s), 19.5 (s), 22.0 (s), 37.0 (t), 41.4 (s), 118.3 (s), 120.6 (s), 121.3 (t), 126.7 (s), 127.8 (s), 128.3 (s), 128.4 (s), 128.8 (s), 128.9 (s), 129.3 (s), 129.8 (s), 130.6 (s), 130.8 (s), 134.1 (s), 134.6 (s), 138.0 (t), 139.7 (s), 140.8 (s), 149.1 (s), 164.7 (s), 166.0 (s), 168.0 (s). FAB-MS m/z: 596 (M^++1). *Anal.* Calcd for $C_{34}H_{31}N_5O_3F_2$: C, 68.56; H, 5.25; N, 11.76; F, 6.38. Found: C, 68.48; H, 5.35; N, 11.80; F, 6.42.

(*Z*)-4′-({4,4-Difluoro-5-[(*N*,*N*-dimethylcarbamoyl)methylene]-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl}carbonyl)-2-(2-ethyl-1*H*-1-imidazol-1-yl)benzanilide Monohydrochloride (9g) The free amine of **9g** was dissolved in EtOH (10 ml), and to this ice-cooled solution was added 4 M HCl/AcOEt (0.2 ml). After removing the volatiles, the residue was recrystallized from MeOH–AcOEt and dried to give **9g** (81%) as a colorless powder. mp 189—191 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.16 (3H, t, J=8 Hz), 2.40 (1H, br), 2.70 (2H, br), 2.88 (3H, s), 3.03 (3H, s), 3.09 (1H, br), 3.40 (1H, br), 4.83 (1H, br), 6.79 (1H, s), 6.81 (1H, s), 7.06 (2H, d, J=7 Hz), 7.17 (2H, t, J=8 Hz), 7.30 (1H, t, J=8 Hz), 7.45 (2H, d, J=7 Hz), 7.70—7.81 (5H, m), 7.93 (1H, m), 10.82 (1H, s). FAB-MS m/z: 584 (M^++1). *Anal.* Calcd for $C_{33}H_{31}N_5O_3F_2\cdot HCl\cdot 0.5H_2O$: C, 63.00; H, 5.29; N, 11.13; F, 6.04; Cl, 5.64. Found: C, 63.06; H, 5.24; N, 11.11; F, 5.74; Cl, 5.98.

(*Z*)-4′-({4,4-Difluoro-5-[(*N*,*N*-diethylcarbamoyl)methylene]-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl}carbonyl)-2-(2-ethyl-1*H*-1-imidazol-1-yl)benzanilide (9h) Colorless powder. Yield: 76%. mp 245—247 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.13 (3H, t, J=8 Hz), 1.19 (3H, t, J=8 Hz), 1.22 (3H, t, J=8 Hz), 2.48 (4H, q, J=8 Hz), 2.60 (1H, br), 3.22 (1H, br), 3.47 (3H, m), 5.00 (1H, br), 6.38 (1H, s), 6.66 (1H, d, J=7 Hz), 6.83 (1H, s), 7.05—7.12 (5H, m), 7.20—7.23 (2H, m), 7.26 (1H, s), 7.31—7.35 (2H, m), 7.62 (2H, m), 8.10 (1H, m). FAB-MS m/z: 612 (M^++1). *Anal.* Calcd for $C_{34}H_{31}N_5O_3F_2\cdot 0.75H_2O$: C, 67.24; H, 5.88; N, 11.20; F, 6.08. Found: C, 67.15; H, 5.76; N, 11.23; F, 6.04.

(*Z*)-4′-({4,4-Difluoro-5-[2-oxo-2-(1-piperidinyl)ethylidene]-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl}carbonyl)-2-(2-ethyl-1*H*-imidazol-1-yl)benzanilide Monohydrochloride (9i) Colorless powder. Yield: 88%. mp 232—235 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.16 (3H, t, J=8 Hz), 1.47 (2H, br), 1.52 (1H, br), 1.60 (2H, d, J=8 Hz), 2.40 (1H, br), 2.70 (2H, d, J=8 Hz), 3.09 (1H, br), 3.47 (6H, br), 4.84 (1H, br), 6.79 (2H, s), 7.06 (2H, d, J=7 Hz), 7.16 (1H, t, J=8 Hz), 7.29 (1H, t, J=8 Hz), 7.45—7.48 (3H, m), 7.70—7.80 (5H, m), 7.95 (1H, m), 10.83 (1H, s). FAB-MS m/z: 624 (M^++1). *Anal.* Calcd for $C_{36}H_{35}N_5O_3F_2\cdot HCl\cdot 0.3H_2O$: C, 64.97; H, 5.54; N, 10.52; F, 5.71; Cl, 5.33. Found: C, 64.78; H, 5.66; N, 10.47; F, 5.98; Cl, 5.36.

(*Z*)-4′-[(4,4-Difluoro-5-{[*N*-(2-methoxyethyl)carbamoyl]methylene}-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl)carbonyl]-2-(2-ethyl-1*H*-1-imidazol-1-yl)benzanilide Monohydrochloride (9j) The free amine of **9j** was dissolved in EtOH (10 ml), and to this ice-cooled solution was added 4 M HCl/AcOEt (0.2 ml). After removing the volatiles, the residue was recrystallized from 2-propanol–Et_2O and dried to give **9j** (48%) as a colorless powder. mp 203—205 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.13 (3H, t, J=8 Hz), 2.35 (1H, br), 2.72 (2H, br), 3.05 (2H, br), 3.27 (3H, s), 3.38 (4H, br), 4.89 (1H, br), 6.52 (1H, s), 6.74 (1H, d, J=7 Hz), 7.08 (2H, d, J=7 Hz), 7.12 (1H, t, J=8 Hz), 7.26 (1H, t, J=8 Hz), 7.34 (1H, d, J=7 Hz), 7.43 (2H, d, J=7 Hz), 7.70—7.79 (5H, m), 7.94 (1H, m), 8.47 (1H, s), 10.82 (1H, s). FAB-MS m/z: 614 (M^++1). *Anal.* Calcd for $C_{34}H_{33}N_5O_4F_2\cdot HCl\cdot 1.5H_2O$: C, 60.31; H, 5.51; N, 10.34; F, 5.61; Cl, 5.24. Found: C, 60.19; H, 5.62; N, 10.42; F, 5.36; Cl, 5.57.

(*Z*)-4′-{[4,4-Difluoro-5-(2-morpholino-2-oxoethylidene)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]carbonyl}-2-(2-ethyl-1*H*-imidazol-1-yl)benzanilide Monohydrochloride (9k) The free amine of **9k** was dissolved in EtOH (10 ml), and to the ice-cooled solution was added 4 M HCl/AcOEt (0.2 ml). After removing the volatiles, the residue was recrystallized from EtOH–Et_2O and dried to give **9k** (54%) as a colorless powder. mp 220—222 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.15 (3H, t, J=8 Hz), 2.42 (1H, br), 2.70 (2H, br), 3.09 (2H, br), 3.51—3.61 (8H, m), 4.85 (1H, br), 6.79 (1H, s), 6.82 (1H, d, J=7 Hz), 7.05 (2H, d, J=7 Hz), 7.17 (1H, t, J=8 Hz), 7.27 (1H, t, J=8 Hz), 7.45—7.50 (3H, m), 7.70—7.80 (5H, m), 7.95 (1H, m), 10.82 (1H, s). FAB-MS m/z: 626 (M^++1). *Anal.* Calcd for $C_{35}H_{33}N_5O_4F_2\cdot HCl\cdot 0.5H_2O$: C, 62.64; H, 5.26; N, 10.44; F, 5.66; Cl, 5.28. Found: C, 62.75; H, 5.26; N, 10.45; F, 5.35; Cl, 5.22.

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