Synthesis and Characterization of Orally Active Nonpeptide Vasopressin V_2 Receptor Antagonists

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The present study was undertaken to evaluate whether a novel series of 2,6-diaza-5-oxobicyclo[5.4.0]undeca-1(7),8,10-triene derivatives exhibited antagonistic activity for vasopressin V_1 and V_2 receptors. Most of these compounds were synthesized and showed a high affinity potential for V_2 receptor and low to moderate affinity potential for V_1 receptor. The most potent and V_2-selective compound, *N*-[4-[2,6-diaza-6-[2-(4-methylpiperazinyl)-2-oxoethyl]-5-oxobicyclo[5.4.0]undeca-1(7),8,10-trien-2-yl]-carbonyl]phenyl][2-(4-methylphenyl)phenyl]-formamide (11b), exhibited IC_{50}'s of 2.9 nM for the V_2 receptor and 200 nM for the V_1 receptor, respectively.

When administered orally to rat, 11b showed an approximately 18-fold increased urine volume in comparison with control rat.

Key words vasopressin; antagonist; anti-diuretic; nonpeptide

Arginine vasopressin (AVP), a cyclic nonapeptide, is produced and secreted from the hypothalamo-neurohypophysial system in response to increased plasma osmolarity detected by brain osmoreceptors and decreased blood volume and blood pressure.[3] AVP contributes to regulation of water and solute excretion by the kidney and to cardiovascular regulation, such as blood pressure control, platelet aggregation and factor VIII secretion.[4]

Two V_1 receptor subtypes (V_{1a}, V_{1b}) have been identified and shown to mediate phospholipase C activation and intracellular calcium mobilization. V_{1b} receptors contribute to the stimulating action on ACTH secretion,[5] but most of known AVP actions are believed to be mediated by V_{1a} receptors.[6] In the kidney, AVP exerts an antidiuretic effect through V_2 receptors *via* an adenosine 3′,5′-cyclic monophosphate (c-AMP) dependent mechanism.[7] Therefore, an AVP V_2 receptor antagonist has long been recognized as a water diuretic.

Water diuretics have exciting therapeutic implications in the management of patients with excess water and consequent hypotonic hyponatremia, as in patients with the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and certain stages of congestive heart failure or liver cirrhosis.[8] However, the most traditional loop diuretic, furosemide, increases sodium excretion concomitant with water excretion, and the elevation of sodium levels in plasma is a clinical disadvantage for this class of drugs.

Therefore, there is an obvious need to develop solute free water diuretics that antagonize osmoregularity. AVP V_2 receptor antagonist may be a useful drug for treating disease in which water is retained.

Since the 1970s, a number of peptide AVP antagonists have been reported.[9] However, the development of such compounds has been limited because of lack of oral bioavailability and/or partial agonistic effects in man.[10] Therefore, there is an obvious need to develop a potent and selective V_2 receptor antagonist that can be orally administered in a clinical setting. In the 1990s, a number of nonpeptide antagonists have been reported: the V_1 selective OPC-21268[11] and SR-49059,[12] and the V_2 selective OPC-31260[13] and SR-121463A[14] (Fig. 1). These reports prompted us to initiate a program to discover novel potent V_2 receptor antagonists. We wish to report herein our studies on a benzodiazepinone series of orally active V_2 antagonists.

Chemistry

The generalized synthetic pathway for the preparation of benzamide derivatives is shown in Chart 1. The target compounds listed in Table 1 were obtained using the corresponding bicyclic amine as according to this route. Benzene-fused hetero ring compounds (**1a**—**e**)[15—18] were converted into the amides (**2a**—**e**)[14] with *p*-nitrobenzoyl chloride. Reduction of the nitro group of **2a**—**e** using iron gave the amides (**3a**—**e**)[19] quantitatively. **3a**—**e** were then acylated with the commercially available carboxylic acids (**5a**—**c**) or readily synthesized carboxylic acids (**5d**,[20] **5e**,[21] **5f**[22]) *via* acid chloride or mixed anhydride to give the target amides (**4a**—**j**).

The synthetic route for the compounds listed in Tables 2 and 3 is summarized in Charts 2—4. The amide (**2d**) was alkylated with ethyl bromoacetate in the presence of sodium hydride to give the ester (**6**). Iron mediated reduction of the nitro group of **6** gave the aniline (**7**) quantitatively. The aniline (**7**) was acylated with the corresponding acid chlorides,

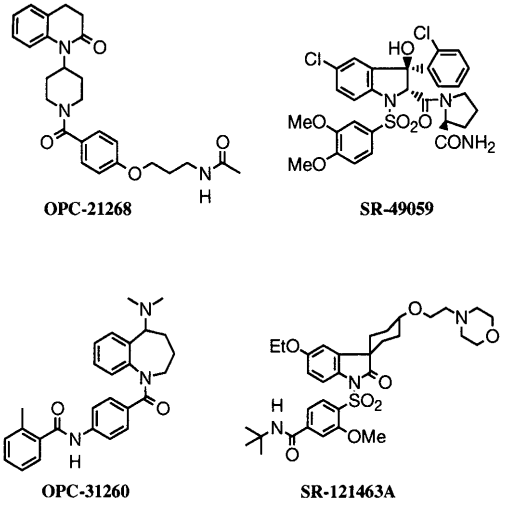

Fig. 1

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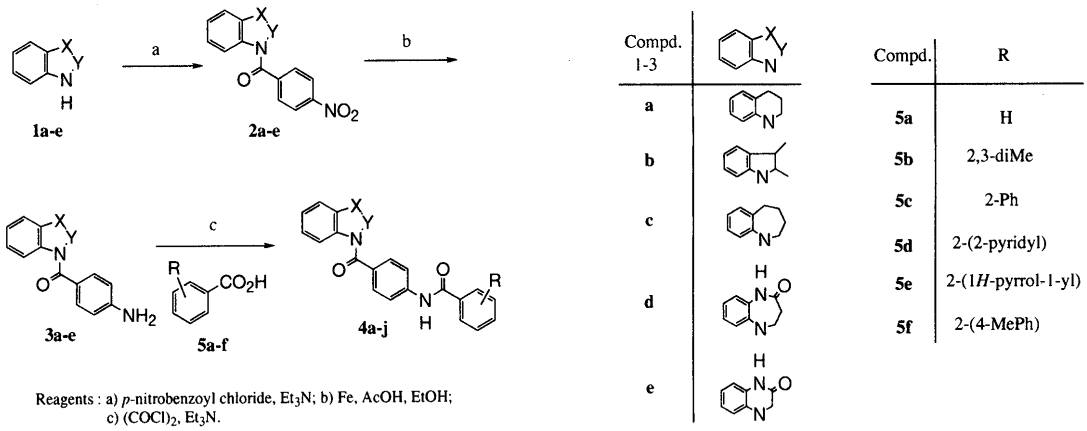
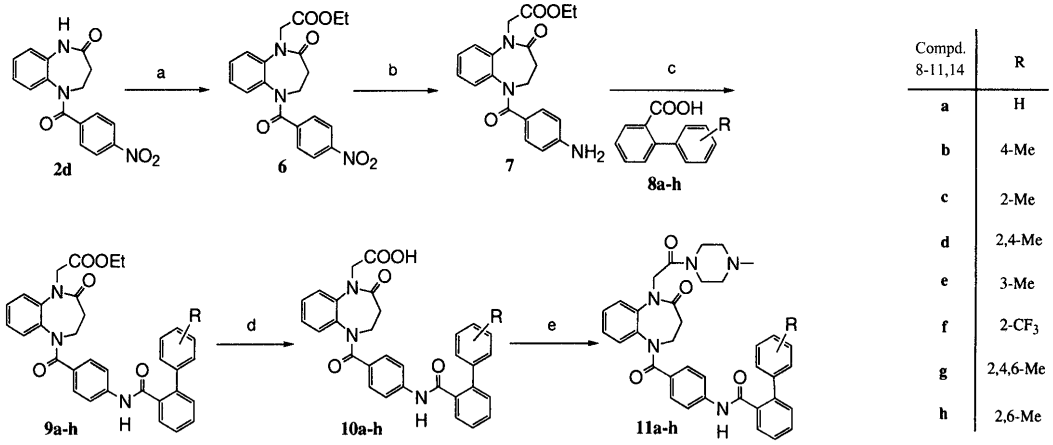


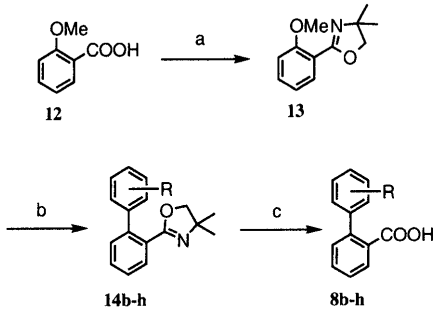
Reagents : a) *p*-nitrobenzoyl chloride, Et_3N; b) Fe, AcOH, EtOH; c) $(COCl)_2$, Et_3N.

Chart 1



Reagents: a) Ethyl bromoacetate, 60% NaH, DMF; b) Fe, AcOH EtOH; c) $(COCl)_2$, Et_3N; d) 1 N NaOH, EtOH; e) *N*-methylpiperazine, WSCD·HCl, HOBt, DMF.

Chart 2



Reagents : a) Ref. 23 b) substituted bromobenzene, Mg, I_2; c) 6N HCl

Chart 3

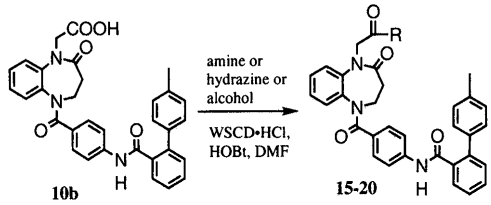


Chart 4

which were prepared from the commercially available biphenylcarboxylic acid or synthesized substituted biphenylcarboxylic acid in the presence of oxalyl chloride, to give the amides (**9a**—**h**). For efficient construction of a wide variety of biphenylcarboxylic acids, we chose coupling of a methoxyoxazoline (**13**) which was prepared by Meyers method[23] with substituted phenyl Grignard reagent to give biphenyl compounds (**14b**—**h**). Subsequent acid hydrolysis of the oxazoline moiety of **14b**—**h** gave biphenyl carboxylic acids (**8b**—**h**) (Chart 3).[24] The esters (**9a**—**h**) were hydrolyzed with 1 N sodium hydroxide to provide carboxylic acids (**10a**—**h**). Amide formation was carried out using 1-ethyl-3-(dimethylaminopropyl) carbodiimide hydrochloride (WSCD·HCl) and 1-hydroxybenzotriazole (HOBt) in *N*,*N*-dimethylformamide (DMF) to give the target amide derivatives (**11a**—**h**) (Chart 2).

Acetamide derivatives (**15**—**19**) or acetate (**20**) listed in Table 2 were obtained from **10b** in the same manner as described for **11b** using the corresponding amine, hydrazine or alcohol, instead of *N*-methylpiperazine (Chart 4). Alternatively, certain aminoalkyl compounds (**21a**, **b**) were prepared by alkylation of key intermediate (**2d**) with the corresponding alkyl halide in the presence of sodium hydride. Corresponding **23a** and **23b**, listed in Table 2, were synthesized by the same procedure as described for **11** (Chart 5).

Results and Discussion

The first non-peptide V_2-selective antagonist, OPC-31260,[14] was disclosed in 1992 and the structure–activity re-

lationship (SAR) were discussed. On the basis of published data, we summarized the following SAR: 1) A dimethylamino group is not necessary for *in vitro* AVP binding affinity. 2) Substituents on the terminal phenyl group influence *in vivo* AVP antagonistic activity. 3) The two amide linkages are essential for affinity to AVP receptors.

To identify suitable novel bicyclic amine (**1**) and R in the parent skeleton (**4**), various bicyclic amine (**1a—e**) and substituents R were introduced and the results are summarized in Table 1. When bicyclic amine was tetrahydroquinoline (**4a**—

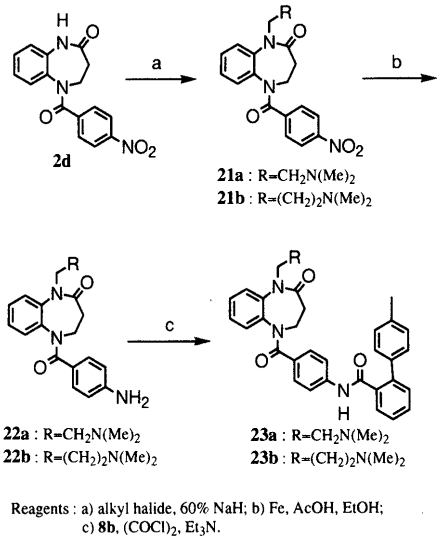
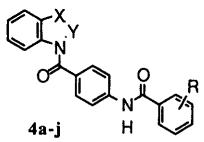


Chart 5

Table 1. The Binding Affinities for V_1 and V_2 Vasopressin Receptors for Formamide (**4a—j**)

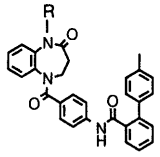


4a-j

No.		R	Binding assay V_1 (rat liver)	IC_{50} (nM)[a] V_2 (rat kidney)
4a		H	1100	540
4b		2,3-diMe	2500	67
4c		2-Ph	44	24
4d		2-(2-Py)	320	28
4e		2-(1*H*-Pyrrol)	130	160
4f		2-(4-MePh)	61	<10
4g		2-(4-MePh)	7100	68
4h		2-(4-MePh)	3.9	3.5
4i		2-(4-MePh)	53	3.2
4j		2-(4-MePh)	170	3

a) See Experimental section: *in vitro* receptor binding assays.

Table 2. Receptor Binding Affinities and Diuretic Effects for Benzodiazepinone Derivatives



No.	R	Binding assay V_1 (rat liver)	IC_{50} (nM) V_2 (rat kidney)	Selectivity V_1/V_2[a]	Rat UV (%)[b]
4i	–H	53	3.2	17	890[c]
10b		440	14	31	NT[d]
11b		200	2.9	69	1830
15		28	1.1	25	740
16		42	1.8	23	180
17		150	4.2	35	1180
18		28	0.27	103	280
19		190	1.8	11	900
20		36	2.4	15	850
23a		208	4.2	50	1470
23b		79	1.7	46	630

a) Selectivity was calculated by dividing the IC_{50} values for V_1 by the IC_{50} values for V_2. *b*) UV values are indicated as ratio (%) of urine volume in control rat for 0 to 3 h, after test compounds were administered orally at a dose of 10 mg/kg. *c*) The data was obtained at a dose of 32 mg/kg. *d*) NT: Not tested.

Table 3. Receptor Binding Affinities and Diuretic Effects for Compounds **11a—h**

No.	R	Binding assay V_1 (rat liver)	IC_{50} (nM) V_2 (rat kidney)	Selectivity V_1/V_2 [a]	Rat UV (%) [b]
11a	H	16	1.8	9	280
11b	4-Me	200	2.9	69	1830
11c	2-Me	3.3	3.1	1	390
11d	2,4-Me	23	2.3	10	1700
11e	3-Me	150	3.0	50	440
11f	2-CF_3	16	15	1	760
11g	2,4,6-Me	NT [c]	41	—	100
11h	2,6-Me	1.8	15	0.1	140

a) See Table 2. *b*) See Table 2. *c*) NT: Not tested.

f), 2-phenyl benzoyl derivatives (**4c**, **f**) displayed similar and potent affinities for both V_1 and V_2 receptors.

Replacement of tetrahydroquinoline by other 6-6 or 6-7 fused ring systems showed that tetrahydrobenzazepine (**4h**), tetrahydrobenzodiazepinone (**4i**), and tetrahydroquinoxaline (**4j**) derivatives were favorable for high V_2 affinity. On the other hand, a 6-5 fused ring system indoline (**4g**) resulted in a slightly decreased V_2 affinity and very weak V_1 affinity. However, none of these compounds showed oral activity. These results prompted us to investigate SAR further.

We hypothesized that the poor water solubility of these compounds resulted in low absorption from the gastrointestinal duct. So we planned to introduce the hydrophilic functional group into **4** series. From the previous SAR, compound **4i** was selected as a starting compound, which showed high V_2 affinity potential and moderate V_1 affinity potential. In addition, **4i** could be easily synthesized in a few steps and had an amide unit which may serve as an ideal scaffold for introducing other functional elements to get the desired water solubility. Various side chains were introduced to the 5-position of the benzodiazepinone ring for the purpose of obtaining oral activity. It appears that all alkylamino (**23a**, **b**) and acetamido (**11b**, **15**—**19**) and acetate (**20**) substituted derivatives have similar V_2 affinity as the unsubstituted **4i**, except for **18**. In contrast, carboxylic acid (**10b**) showed a significant reduction in affinity for both receptors. The results of examination of oral activity are shown in Table 2 based on the measurement of urine volume in rats. Some derivatives could be improved in *in vivo* activity by introducing the hydrophilic amino substituent into the parent skeleton (**4i**). The effects of these amino substituents were critical, a ten fold difference between **11b** and **16** was observed, even though *in vitro* activity was similar. Compound **11b** showed promising diuretic activity. It was assumed that the amino substituent was able to participate effectively in absorption from gastrointestinal duct. Encouraged by these results, a similar modification was examined with tetrahydroquinoxaline (**4j**). Unfortunately, an orally active compound was not obtained in these series (data not shown).

We then examined the influence of substituents on the terminal 2-phenyl moiety, which had a large effect on receptor binding affinities (Table 3). Introduction of a large alkyl group such as ethyl and isopropyl or an electron-withdrawing group such as nitro decreased V_2 affinity (not shown), so we examined the substituent effect of a small methyl group on the 2-phenyl ring. Adding methyl to the 4 position (**11b**, **d**) or 3 position (**11e**) led to higher V_2 selectivity, which was

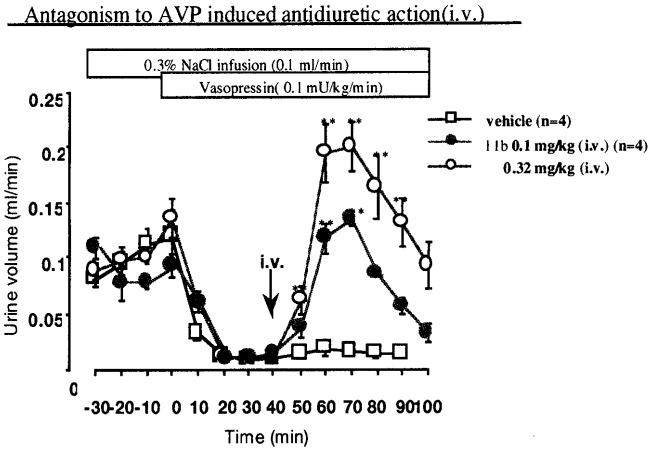


Fig. 2. *In Vivo* Activities of Compound **11b** in Rats

Values are expressed as mean±S.E. $*p<0.05$; $**p<0.01$ *vs.* vehicle (Dunnett's test).

calculated by dividing the IC_{50} values for V_1 by the IC_{50} values for V_2, since these substituents reduced V_1 affinity potential and showed similar affinity potential for V_2 compared with the unsubstituted case (**11a**). In addition, **11b** and **11d** exhibited potent oral diuretic activity. This result demonstrated that a methyl group at the 4 position induced good oral absorption.

Enhancement of V_1 binding affinity was observed by introduction of a 2-methyl group, for example, **11c**. However, compounds having a 2-methyl substituent (**11c**, **g**, **h**) lacked oral activity.

The structure–activity relationships could be summarized as follows: 1) The terminal 4-methylphenyl substituent played an important role in high V_2 selectivity and oral activity. 2) A benzodiazepinone (**4i**) or tetrahydroquinoxaline (**4j**) skeleton was found to provide potent V_2 binding affinity. 3) Some amino substituted derivatives such as **11b**, **17** and **23a** dramatically increased the oral activity.

On the basis of these structure–activity relationships, **11b** was selected for investigation of further *in vivo* activity. Initially, the antagonistic effect on AVP induced antidiuretic action was evaluated. Intravenous administration of **11b** dose-dependently inhibited the anti-diuretic action of exogenously administered AVP in rats (Fig. 2). The aquaretic effect was then examined. In normally hydrated conscious rats, oral administration of **11b** at 1 to 10 mg/kg induced both an increase of urine volume and a decrease of urine osmolarity in a dose-dependent manner (Fig. 3).

In conclusion, we have obtained a highly selective series of vasopressin V_2 receptor antagonists, represented by **11b**, which bound 70 times more potently to the V_2 receptor than the V_1 receptor. The affinity for the V_2 receptor was about 6 fold more potent than OPC-31260 (V_1, 710 nM; V_2, 17 nM).[13] In a rat model, **11b** showed an oral diuretic effect and decreased urine osmolarity. These data suggest the possible therapeutic usefulness of the V_2 selective antagonist (**11b**) in water-retaining diseases, such as congestive heart failure.

Experimental

Melting points were determined on a capillary melting point apparatus (Thomas Hoover) and were uncorrected. ^{1}H-NMR spectra were measured at 200 MHz on a Bruker 200 spectrometer. Chemical shifts were reported in δ (ppm) units using tetramethylsilane as internal standard. Mass spectra were recorded on a VG (Fisons) ZAB-SE (FAB). Elemental analyses were per-

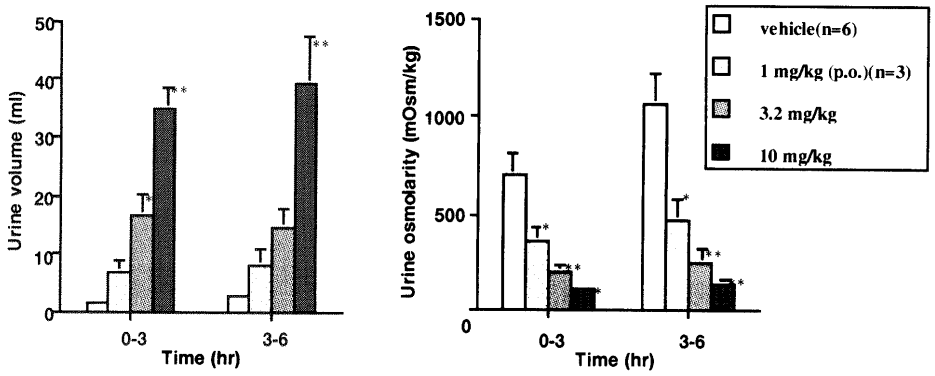


Fig. 3. *In Vivo* Aquaretic Effects (p.o.) of Compound **11b**.

Values are expressed as mean±S.E. $*p<0.05$; $**p<0.01$ *vs.* vehicle (Dunnett's test).

formed on a Perkin–Elmer 2400 CHN analyzer. Chromatography was performed on silica gel (Merck Kieselgel 60, 70—230 mesh) using the indicated solvent mixtures. The starting materials were commercially available (**1a**, **5a**—**c**) or were prepared by known methods.

Ethyl 2-[2,6-Diaza-6-[(4-nitrophenyl)carbonyl]-3-oxobicyclo[5.4.0]-undeca-1(7),8,10-trien-2-yl]acetate (6) To a suspension of sodium hydride (154 mg, 3.85 mmol, 60% w/w in mineral oil) in tetrahydrofuran (4 ml) was added a solution of 2,6-diaza-6-[(4-nitrophenyl)carbonyl]bicyclo-[5.4.0]undeca-1(7),8,10-trien-3-one (**2d**), (800 mg, 2.57 mmol) in tetrahydrofuran (6 ml) at 0 °C and the mixture was stirred at 0 °C for 5 min. Ethyl bromoacetate (472 mg, 2.82 mmol) was added to the mixture and the mixture was stirred at room temperature overnight. The reaction mixture was quenched with saturated aqueous ammonium chloride and diluted with ethyl acetate. The organic layer was washed with saturated aqueous sodium bicarbonate and brine, and the organic layer was dried ($MgSO_4$) and concentrated to give **6** (691 mg, 68%) as a slight yellow amorphous solid. ^{1}H-NMR ($CDCl_3$) δ: 1.33 (3H , t, J=7 Hz), 2.62—2.90 (2H, m), 3.90 (1H, ddd, J=1, 7, 13 Hz), 4.29 (2H, ddd, J=1, 7, 15 Hz), 4.50 (1H, d, J=16 Hz), 4.70 (1H, d, J=16 Hz), 4.65—4.90 (1H, m), 6.72 (1H, d, J=9 Hz), 6.90—7.02 (1H, br), 7.23—7.37 (2H, m), 7.50 (2H, d, J=9 Hz), 8.03 (2H, d, J=9 Hz). FAB-MS *m/z*: 398 $(M+H)^+$.

Ethyl 2-[6-[(4-Aminophenyl)carbonyl]-2,6-diaza-3-oxo-bicyclo[5.4.0]-undeca-1(7),8,10-trien-2-yl]acetate (7) To a solution of **6** (667 mg, 1.68 mmol) in methanol (10 ml) were added iron powder (469 mg, 8.40 mmol) and acetic acid (1 ml), and the mixture was stirred at reflux temperature for 1 h. Insoluble material was removed by filtration through a bed of Celite and the filtrate was concentrated *in vacuo*. The residue was diluted with chloroform and saturated aqueous sodium bicarbonate and insoluble material was again removed by filtration through a bed of Celite. The organic layer was separated and washed with water and brine. The solution was dried ($MgSO_4$) and concentrated. The crude product was crystallized with diisopropyl ether–hexane (1 : 1) to give **7** (610 mg, 99%) as slight brown crystals, mp 80—83 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, t, J=7 Hz), 2.56—2.88 (2H, m), 3.78—3.90 (3H, br s), 4.15—4.35 (3H, m), 4.60—4.80 (1H, m), 4.83 (1H, d, J=16 Hz), 6.39 (2H, d, J=9 Hz), 6.80 (1H, d, J=9 Hz), 6.95—7.05 (2H, m), 7.03 (1H, d, J=9 Hz), 7.26 (2H, s). FAB-MS *m/z*: 368 $(M+H)^+$.

Ethyl 2-[2,6-Diaza-6-[[4-[[2-(4-methylphenyl)phenyl]carbonyl-amino]-phenyl]carbonyl]-3-oxobicyclo[5.4.0]undeca-1(7),8,10-trien-2-yl]acetate (9b) To a mixture of 2-(4-methylphenyl)benzoic acid (**5f**), (258 mg, 1.20 mmol) and oxalyl chloride (0.2 ml) in dichloromethane (5 ml) was added 1 drop of DMF and the mixture was stirred at 0 °C for 0.5 h. After solvent was removed by evaporation, the residual acid chloride was dissolved in dichloromethane (5 ml) and the solution was added to a mixture of **7** (440 mg, 1.20 mmol) and triethylamine (243 mg, 2.40 mmol) in dichloromethane (5 ml). The mixture was stirred at room temperature for 3 h then washed successively with 0.5 N HCl, saturated aqueous sodium bicarbonate, brine and dried ($MgSO_4$). The solvent was concentrated and the residue was purified by silica gel column chromatography (AcOEt : hexane= 3 : 2) to give **9b** (274 mg, 41%) as white crystals, mp 120—125 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, t, J=8 Hz), 2.37 and 2.40 (total 3H, s), 2.25—2.90 (2H, m), 3.83 (1H, dd, J=6, 13 Hz), 4.18—4.35 (3H, m), 4.60—4.90 (2H, m), 6.75 (1H, d, J=8 Hz), 6.95 (4H, d, J=9 Hz), 7.08—7.58 (11H, m), 7.82 (1H, dd, J=1, 9 Hz). FAB-MS *m/z*: 562 $(M+H)^+$.

Compounds **9a** and **9c**—**i** were synthesized in the same manner as described for **9b**.

Spectral data are summarized in Table 5.

2,6-Diaza-6-[(4-nitrophenyl)carbonyl]bicyclo[5.4.0]undeca-1(7),8,10-trien-3-one (2d) To a solution of 2,6-diazabicyclo[5.4.0]undeca-1(7),8,10-trien-3-one(**1d**)[17] (0.87 g, 5.36 mmol) and triethylamine (0.55 g, 5.45 mmol) in dichloromethane (5 ml) was added a solution of 4-nitrobenzoyl chloride (1.00 g, 5.39 mmol) in dichloromethane (5 ml) at 0 °C. After stirring at room temperature for 2 h, the mixture was washed successively with 0.5 N HCl, saturated aqueous sodium bicarbonate and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was crystallized with diethyl ether–diisopropyl ether (1 : 1) to give **2d** (1.60 g, 95%) as slight brown crystals , mp 225—230 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.61—3.00 (2H, m), 3.90 (1H, br), 4.89 (1H, br), 6.71 (1H, d, J=8 Hz), 6.90 (1H, t, J=8 Hz), 7.01—7.77 (2H, m), 7.35 (2H, d, J=8 Hz), 8.02 (2H, d, J=8 Hz), 8.52 (1H, s). FAB-MS *m/z*: 312 $(M+H)^+$.

2,3-Dimethylindolinyl 4-Nitrophenyl Ketone (2b) The title compound was prepared in a similar manner to that described for **2d** using **1b**[15] instead of **1d**. Pale yellow crystals. ^{1}H-NMR ($CDCl_3$) δ: 1.18 (3H, d, J=7 Hz), 1.31 (3H, d, J=7 Hz), 3.59 (1H, dq, J=7, 7 Hz), 4.77 (1H, dq, J=7, 7 Hz), 7.15—7.45 (6H, m), 7.63 (1H, d, J=8 Hz). FAB-MS *m/z*: 312 $(M+H)^+$.

4-[(4-Nitrophenyl)carbonyl]-1,3,4-trihydroquinoxalin-2-one (2e) The title compound was prepared in a similar manner to that described for **2d**, using 1,3,4-trihydroquinoxalin-2-one (**1e**)[18] instead of benzodiazepinone (**1d**). White amorphous solid. ^{1}H-NMR (DMSO-d_6) δ: 4.43 (2H, s), 6.73 (2H, br), 7.00—7.16 (2H, m), 7.64 (2H, d, J=8 Hz), 8.20 (2H, d, J=8 Hz). FAB-MS *m/z*: 298 $(M+H)^+$.

4-Aminophenyl 1,2,3,4-Tetrahydroquinolyl Ketone (3a) The title compound was prepared in a similar manner to that described for **7** using **2a** instead of **6**. Pale yellow crystals, mp 205—208 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.05 (2H, m), 2.82 (2H, dd, J=7, 7 Hz), 3.88 (2H, dd, J=7, 7 Hz), 6.48—7.47 (8H, m). FAB-MS *m/z*: 253 $(M+H)^+$.

4-Aminophenyl 2,3-Dimethylindolinyl Ketone (3b) The title compound was prepared in a similar manner to that described for **7** using **3b** instead of **6**. Pale yellow crystals, mp 163—164 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.10 (3H, d, J=7 Hz), 1.27 (3H, d, J=7 Hz), 3.55 (1H, dq, J=7, 7 Hz), 3.94 (2H, br), 4.74 (1H, dq, J=7, 7 Hz), 6.66 (2H, d, J=8 Hz), 6.93—7.03 (3H, m), 7.14 (1H, m), 7.47 (2H, d, J=8 Hz). FAB-MS *m/z*: 267 $(M+H)^+$.

6-[(4-Aminophenyl)carbonyl]-2,6-diazabicyclo[5.4.0]undeca-1(7),8,10-trien-3-one (3c) The title compound was prepared in a similar manner to that described for **7** using **3c** instead of **6**. White prisms, mp 216—221 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.67 (2H, br), 3.90—4.80 (2H, br), 6.38 (2H, d, J= 9 Hz), 6.78 (1H, dd, J=1, 8 Hz), 6.90—7.24 (5H, m). FAB-MS *m/z*: 282 $(M+H)^+$.

4-[(4-Aminophenyl)carbonyl]-1,3,4-trihydroquinoxalin-2-one (3e) The title compound was prepared in a similar manner to that described for **7** using **3e** instead of **6**. White amorphous solid. ^{1}H-NMR (DMSO-d_6) δ: 4.31 (2H, s), 5.71 (2H, br), 6.43 (2H, d, J=8 Hz), 6.69—6.83 (2H, m), 6.98—7.09 (4H, m). FAB-MS *m/z*: 268 $(M+H)^+$.

[2-(1*H*-Pyrrol-1-yl)phenyl]-*N*-[4-(1,2,3,4-tetrahydroquinolyl-carbonyl)phenyl]formamide (4e) To a mixture of 2-(1*H*-pyrrol-1-yl) phenylcarboxylic acid (**5e**)[21] (206 mg, 1.10 mmol), 4-amino-phenyl 1,2,3,4-tetrahydroquinolyl ketone (**3a**), (277 mg, 1.10 mmol) and diphenyl chlorophosphate (325 mg, 1.21 mmol) in tetrahydrofuran (10 ml) was added triethylamine (333 mg, 3.30 mmol) and the mixture was stirred at room temperature for 2 h. The resulting mixture was concentrated and diluted with ethyl acetate.

Table 4. Analytical and Spectral Data for Compounds **4a—j**

Compd. No.	^{1}H-NMR, δ (ppm)	Solvent[a]	FAB-MS *m/z*	mp (°C) Solvent[b]	Formula	Calcd (Found) C	H	N
4a	2.06 (2H, m), 2.85 (2H, dd, *J*=7, 7 Hz), 3.91 (2H, dd, *J*=7, 7 Hz), 6.70 (1H, d, *J*=8 Hz), 6.90 (1H, dd, *J*=8, 8 Hz), 7.00 (1H, dd, *J*=8, 8 Hz), 7.17 (1H, d, *J*=8 Hz), 7.38 (1H, d, *J*=8 Hz), 7.42—7.64 (5H, m), 7.80—8.00 (3H, m)	A	357 $(M+H)^+$	206—208 MeOH	$C_{23}H_{20}N_2O_2$	77.51 (77.55	5.66 5.72	7.86 7.75)
4b	1.94 (2H, m), 2.23 (3H, s), 2.28 (3H, s), 2.81 (2H, dd, *J*=7, 7 Hz), 3.77 (2H, dd, *J*=7, 7 Hz), 6.78 (1H, d, *J*=8 Hz), 6.86—7.09 (2H, m), 7.10—7.40 (7H, m), 7.70 (2H, d, *J*=8 Hz)	B	385 $(M+H)^+$	224—227	$C_{25}H_{24}N_2O_2$ MeOH	78.10 (77.86	6.29 6.33	7.29 7.16)
4c	2.00 (2H, dt, *J*=7, 7 Hz), 2.80 (2H, t, *J*=7 Hz), 3.96 (2H, t, *J*=7 Hz), 6.66 (1H, d, *J*=8 Hz), 6.86 (1H, dt, *J*=8, 2 Hz), 6.93—7.60 (15H, m), 7.89 (1H, dt, *J*=8, 2 Hz)	A	433 $(M+H)^+$	172—175 EtOH–H_2O	$C_{29}H_{24}N_2O_2$	80.53 (80.41	5.59 5.63	6.48 6.25)
4d	2.04 (2H, dt, *J*=7, 7 Hz), 2.83 (2H, t, *J*=7 Hz), 3.89 (2H, t, *J*=7 Hz), 6.72 (1H, d, *J*=7 Hz), 6.87 (1H, dd, *J*=8, 8 Hz), 7.00 (1H, dd, *J*=8, 8 Hz), 7.16 (1H, d, *J*=8 Hz), 7.21—7.65 (9H, m), 7.66—7.88 (2H, m), 8.55—8.66 (1H, m)	A	434 $(M+H)^+$	120—123 AcOEt–Hex	$C_{28}H_{23}N_3O_2$	77.58 (77.29	5.35 5.55	9.69 9.38)
4e	1.94 (2H, dt, *J*=7, 7 Hz), 2.81 (2H, t, *J*=7 Hz), 3.74 (2H, t, *J*=7 Hz), 6.17 (2H, dd, *J*=2, 2 Hz), 6.77 (1H, d, *J*=8 Hz), 6.86—7.10 (4H, m), 7.21 (1H, d, *J*=8 Hz), 7.28 (2H, d, *J*=8 Hz), 7.40—7.70 (6H, m)	B	422 $(M+H)^+$	197—198 AcOEt–Hex	$C_{27}H_{23}N_3O_2$	76.94 (76.99	5.50 5.42	9.97 9.71)
4f	2.03 (2H, dt, *J*=7, 7 Hz), 2.36 (3H, s), 2.82 (2H, t, *J*=7 Hz), 3.88 (2H, t, *J*=7 Hz), 6.67 (1H, d, *J*=8 Hz), 6.87 (1H, dt, *J*=8, 2 Hz), 6.95—7.60 (14H, m), 7.86 (1H, dd, *J*=8, 2 Hz)	A	447 $(M+H)^+$	100—101 Et_2O	$C_{30}H_{26}N_2O_2$	80.69 (80.46	5.87 5.93	6.27 6.12)
4g	1.05 (3H, d, *J*=7 Hz), 1.09 (3H, d, *J*=7 Hz), 2.38 (3H, s), 3.58 (1H, dq, *J*=7, 7 Hz), 4.72 (1H, dq, *J*=7, 7 Hz), 6.97—7.59 (16H, m), 7.99 (1H, dd, *J*=7, 2 Hz)	A	461 $(M+H)^+$	188—190 AcOEt–Hex	$C_{31}H_{28}N_2O_2$	80.84 (80.56	6.13 6.36	6.08 5.81)
4h	1.49 (1H, m), 1.81—2.17 (3H, m), 2.33 (3H, s), 2.64—3.10 (3H, m), 5.00 (1H, m), 6.61 (1H, d, *J*=8 Hz), 6.82—7.55 (15H, m), 7.84 (1H, d, *J*=8 Hz)	A	461 $(M+H)^+$	181—182 MeOH–IPE	$C_{31}H_{28}N_2O_2$	80.84 (80.71	6.13 6.29	6.08 5.93)
4i	2.33 (3H, s), 2.69 (2H, br), 3.73—4.01 (1H, br), 4.53—4.94 (1H, br), 6.72 (1H, d, *J*=8 Hz), 6.85—7.54 (14H, m), 7.80 (1H, dd, *J*=8, 1 Hz), 8.22 (1H, s)	A	476 $(M+H)^+$	183—190 EtOH–H_2O	$C_{30}H_{25}N_3O_3$	75.77 (75.61	5.30 5.50	8.84 8.69)
4j	2.36 (3H, s), 4.56 (2H, s), 6.68 (1H, d, *J*=8 Hz), 6.79 (1H, ddd, *J*=8, 8, 1 Hz), 7.93 (1H, dd, *J*=8, 1 Hz), 7.00—7.13 (3H, m), 7.19—7.59 (9H, m), 7.88 (1H, dd, *J*=8, 1 Hz), 8.57 (1H, br)	A	462 $(M+H)^+$	230—231 MeOH	$C_{29}H_{23}N_3O_3$	75.47 (75.29	5.02 5.27	9.10 9.01)

a) A, $CDCl_3$; B, DMSO-d_6. *b*) Recrystallization solvent: Hex, hexane; IPE, diisopropyl ether.

The organic layer was washed successively with water , saturated aqueous sodium bicarbonate and brine. The solvent was dried ($MgSO_4$), filtered, and concentrated. The crude product was triturated with EtOH to give **4e** (280 mg, 60%) as pale yellow crystals, mp 197—198 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.94 (2H, dt, *J*=7, 7 Hz), 2.81 (2H, t, *J*=7 Hz), 3.74 (2H, t, *J*=7 Hz), 6.17 (2H, dd, *J*=2, 2 Hz), 6.77 (1H, d, *J*=8 Hz), 6.86—7.10 (4H, m), 7.21 (1H, d, *J*=8 Hz), 7.28 (2H, d, *J*=8 Hz), 7.40—7.70 (6H, m). FAB-MS *m/z*: 422 $(M+H)^+$.

Compounds **4a—d** and **4f—j** were synthesized in the same manner as described for **4e**.

Analytical and spectral data are summarized in Table 4.

2-(2-Pyridyl)benzoic Acid (5d) To a solution of methyl 2-(2-pyridyl) benzoate[20] (500 mg, 2.34 mmol) in tetrahydrofuran (10 ml) was added 1 N aqueous sodium hydroxide solution (2.8 ml) and the mixture was stirred at 65 °C for 3 h. The reaction mixture was concentrated and the residue was dissolved in water. The aqueous solution was acidified with 1 N hydrochloric acid and extracted with chloroform. The organic layer was separated and dried over ($MgSO_4$). The solvent was concentrated to give **5d** (400 mg, 86%) as pale yellow crystals, mp 162—165 °C. ^{1}H-NMR (DMSO-d_6) δ: 7.35 (1H, m), 7.44—7.62 (4H, m), 7.68 (1H, d, *J*=8 Hz), 7.85 (1H, dd, *J*=8, 8 Hz), 8.58 (1H, m). FAB-MS *m/z*: 200 $(M+H)^+$.

2-[2,6-Diaza-6-[[4-[[2-(4-methylphenyl)phenyl]carbonylamino]-phenyl]-carbonyl]-3-oxobicyclo[5.4.0]undeca-1(7),8,10-trien-2-yl]acetic Acid (10b) To a solution of **9b** (240 mg, 0.427 mmol) in ethanol (5 ml) was added 1 N aqueous sodium hydroxide solution (2 ml) and the mixture was stirred at room temperature for 1 h . The reaction mixture was concentrated and the residue was dissolved in ethyl acetate and 1 N HCl . The solution was extracted with chloroform, washed with brine and dried ($MgSO_4$). The solvent was concentrated and triturated with diisopropyl ether–diethyl ether (1 : 1) to give **10b** (217 mg, 95%) as white crystals, mp 175—183 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.36 (3H, s), 2.52—2.82 (2H, m), 3.82 (1H, dd, *J*=6, 13 Hz), 4.42 (1H, d, *J*=17 Hz), 4.55—4.86 (2H, m), 6.65—6.80 (1H, m), 6.90—7.58 (14H, m), 7.75 (1H, d, *J*=8 Hz). FAB-MS *m/z*: 534 $(M+H)^+$. *Anal.* Calcd for $C_{32}H_{27}N_3O_5$: C, 72.03; H, 5.10; N, 7.88. Found: C, 71.99; H, 5.29; N, 7.65.

Compounds **10a** and **10c—i** were synthesized in the same manner as described for **10b**.

Spectral data are summarized in Table 6.

***N*-[4-[2,6-Diaza-6-[2-(4-methylpiperazinyl)-2-oxoethyl]-5-oxobicyclo-[5.4.0]undeca-1(7),8,10-trien-2-yl]carbonyl]phenyl][2-(4-methyl-phenyl)phenyl]formamide (11b)** To a mixture of **10b** (90 mg, 0.169 mmol), *N*-methylpiperazine (17 mg, 0.170 mmol) and HOBt (27 mg, 0.20 mmol) in DMF (4 ml) was added a solution of WSCD·HCl (39 mg, 0.20 mmol) in DMF (1.0 ml) and the mixture was stirred at room temperature for 1.5 h. The resulting mixture was diluted with ethyl acetate and the organic layer was washed successively with saturated aqueous sodium bicarbonate and brine. The solvent was dried ($MgSO_4$), filtered, and concentrated. The crude product was triturated with diethyl ether–hexane (1 : 1) to give **11b** (100 mg, 96%) as white crystals, mp 161—163 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.35 (3H, s), 2.39 (3H, s), 2.40—2.95 (6H, m), 3.55—3.90 (5H, m), 4.10 (1H, d, *J*=16 Hz), 4.71 (1H, dt, *J*=5, 10 Hz), 5.18 (1H, d, *J*=16 Hz), 6.72 (1H, d, *J*=8 Hz), 6.88—7.60 (14H, m), 7.80 (1H, dd, *J*=1, 8 Hz). *Anal.* Calcd for $C_{37}H_{37}N_5O_4$: C, 72.17; H, 6.06; N, 11.37. Found: C, 72.09; H, 6.21; N, 11.22.

Compounds **11a** and **11c—h** were synthesized in the same manner as described for **11b**.

Analytical and spectral data are summarized in Table 8.

4,4-Dimethyl-2-[2-(2-methylphenyl)phenyl]-1,3-oxazoline (14c) To a suspension of magnesium metal (711 mg, 29 mmol) in tetrahydrofuran (50 ml) at room temperature was added dropwise 2-bromobenzene (5.0 g,

Table 5. Spectral and Physical Data for Compounds **9a—i**

Compd. No.	^{1}H-NMR($CDCl_3$), δ (ppm)	FAB-MS *m/z*	mp (°C) Solvent[a]
9a	1.32 (3H,t, J=7 Hz), 2.62 (1H, m), 2.77 (1H, m), 3.82 (1H, m), 4.14—4.36 (3H, m), 4.62—4.88 (2H, m), 6.71 (1H, d, J=8 Hz), 6.84—7.02 (4H, m), 7.10 (2H, d, J=8 Hz), 7.19—7.60 (9H, m), 7.84 (1H, d, J=8 Hz)	548 $(M+H)^+$	126—128 Et_2O–Hex
9b	1.32 (3H, t, J=8 Hz), 2.37 and 2.40 (total 3H, s), 2.25—2.90 (2H, m), 3.83 (1H, dd, J=6, 13 Hz), 4.18—4.35 (3H, m), 4.60—4.90 (2H, m), 6.75 (1H, d, J=8 Hz), 6.95 (4H, d, J=9 Hz), 7.08—7.58 (11H, m), 7.82 (1H, dd, J=1, 9 Hz)	562 $(M+H)^+$	120—125 Et_2O–Hex
9c	1.33 (3H, t, J =7 Hz), 2.08 (3H, s), 2.55—2.88 (2H, m), 3.85 (1H, dd, J=5, 11 Hz), 4.17—4.35 (3H, m), 4.60—4.83 (1H, m), 4.70 (1H, d, J=17 Hz), 6.73 (1H, d, J=9 Hz), 6.85—7.04 (1H, m), 6.86 (2H, d, J=9 Hz), 7.03—7.19 (3H, m), 7.20—7.43 (6H, m), 7.52 (1H, dt, J=6, 13 Hz), 7.53 (1H, dt, J=6, 13 Hz), 8.08 (1H, dd, J=1, 8 Hz)	548 $(M+H)^+$	127—130 Et_2O–IPE
9d	1.39 (3H, t, J=8 Hz), 2.00 and 2.03 (total 3H, s), 3.37 (3H, s), 2.52—2.85 (2H, m), 3.81 (1H, m), 4.18—4.34 (3H, m), 4.62—4.83 (2H, m), 6.71 (1H, m), 6.86 (2H, d, J=9 Hz), 6.97 (1H, m), 7.08—7.28 (8H, m), 7.44—7.59 (2H, m), 8.07 (1H, dd, J=1, 8 Hz)	576 $(M+H)^+$	Amorphous Solid
9e	1.30 (3H, t, J=7.5 Hz), 2.30 (3H, s), 2.56—2.89 (2H, m), 3.82 (1H, m), 4.17—4.33 (3H, m), 4.62—4.84 (2H, m), 6.72 (1H, d, J=7.5 Hz), 6.89—7.01 (4H, m), 7.08—7.57 (11H, m), 7.85 (1H, dd, J= 7.5, 1.5 Hz)	562 $(M+H)^+$	116—118 Et_2O–Hex
9f	1.30 (3H, t, J=7 Hz), 2.15 (3H, s), 2.36 (3H, s), 2.51—2.92 (2H, m), 3.72—3.93 (1H, m), 4.15—4.39 (3H, m), 4.57—4.79 (1H, m), 4.82 (1H, d, J=17 Hz), 6.72 (1H, brd, J=9 Hz), 6.82—7.48 (14H, m), 7.71 (1H, brd, J=9 Hz)	576 $(M+H)^+$	Amorphous Solid
9g	1.31 (3H, t, J=7.5 Hz), 2.52—2.88 (2H, m), 3.81 (1H, m), 4.15—4.82 (3H, m), 4.68 (1H, m), 4.78 (1H, d, J=17 Hz), 6.70 (1H, d, J=7.5 Hz), 6.90—7.36 (7H, m), 7.43—7.58 (4H, m), 7.77 (2H, m)	616 $(M+H)^+$	Amorphous Solid
9h	1.31 (3H, t, J=7.5 Hz), 1.93 (3H, s), 1.97 (3H, s), 2.37 (3H, s), 2.52—2.89 (2H, m), 3.82 (1H, m), 4.14—4.33 (3H, m), 4.70 (1H, m), 4.81 (1H, d, J=17 Hz), 6.72 (1H, d, J=7.5 Hz), 6.85 (1H, d, J= 8.5 Hz), 6.97 (1H, m), 7.01—7.17 (4H, m), 7.26 (2H, d, J=8.5 Hz), 7.27 (1H, s), 7.44—7.60 (3H, m), 8.27 (1H, m)	590 $(M+H)^+$	Amorphous Solid
9i	1.31 (3H, t, J=7 Hz), 1.99 (3H, s), 2.02 (3H, s), 2.61 (1H, m), 2.26 (1H, m), 3.82 (1H, m), 4.16—4.36 (3H, m), 4.61—4.88 (2H, m), 6.71 (1H, m), 6.84 (2H, d, J=8 Hz), 6.95 (1H, m), 7.08 (2H, d, J=8 Hz), 7.14 (1H, d, J=8 Hz), 7.17—7.36 (5H, m), 7.42 (1H, s), 7.47—7.64 (2H, m), 8.37 (1H, d, J=8 Hz)	576 $(M+H)^+$	161—162 Et_2O

a) Recrystallization solvent: IPE, diisopropyl ether; Hex, hexane.

Table 6. Spectral and Physical Data for Compounds **10a—i**

Compd. No.	^{1}H-NMR, δ (ppm)	Solvent[a]	FAB-MS *m/z*	mp (°C) Solvent[b]
10a	2.41—2.70 (2H, m), 3.72 (1H, m), 4.35—4.55 (2H, m), 4.66 (1H, d, J=16 Hz), 6.82 (1H, d, J=8 Hz), 7.02 (1H, dd, J=8, 8 Hz), 7.15 (2H, d, J=8 Hz), 7.22—7.64 (13H, m)	B	520 $(M+H)^+$	220—222 Et_2O–Hex
10b	2.36 (3H, s), 2.52—2.82 (2H, m), 3.82 (1H, dd, J=6, 13 Hz), 4.42 (1H, d, J=17 Hz), 4.55—4.86 (2H, m), 6.65—6.80 (1H, m), 6.90—7.58 (14H, m), 7.75 (1H, d, J=8 Hz)	A	534 $(M+H)^+$	175—183 IPE–Et_2O
10c	2.10 (3H, s), 2.58—2.85 (2H, m), 3.80 (1H, dd, J=5, 11 Hz), 4.38 (1H, d, J=17 Hz), 4.60—4.90 (3H, m), 6.65—6.75 (1H, brs), 6.80—7.60 (14H, m), 8.00 (1H, d, J=8 Hz)	A	534 $(M+H)^+$	200—205 AcOEt–Hex
10d	2.00 and 2.04 (total 3H, s), 2.35 (3H, s), 2.54—2.86 (2H, m), 3.80 (1H, m), 4.32 (1H, d, J=18 Hz), 4.68 (1H, m), 4.82 (1H, d, J=18 Hz), 6.28 (2H, br), 6.72 (1H, m), 6.87 (2H, d, J=9 Hz), 6.95 (1H, m), 7.02—7.39 (8H, m), 7.42—7.58 (2H, m), 7.99 (1H, d, J=8 Hz)	A	548 $(M+H)^+$	Amorphous Solid
10e	2.27 (3H, s), 2.50—2.82 (2H, m), 3.80 (1H, dd, J=6, 12.5 Hz), 4.38 (1H, d, J=17.7 Hz), 4.53—4.81 (2H, m), 5.48 (1H, br), 6.71 (1H, d, J=7.5 Hz), 6.96 (2H, d, J=8.5 Hz), 7.03—7.29 (10H, m), 7.34—7.53, (3H, m), 7.87 (1H, d, J=7.5 Hz)	A	534 $(M+H)^+$	164—166 Et_2O–Hex
10f	2.12 (3H, s), 2.34 (3H, s), 2.46—2.85 (2H, m), 3.70—3.91 (1H, m), 4.35 (1H, d, J=17 Hz), 4.50—4.77 (1H, m), 4.75 (1H, d, J=17 Hz), 6.60—6.81 (1H, m), 6.83—7.47 (14H, m), 7.61 (1H, brd, J=9 Hz), 8.01—8.41 (1H, m)	A	548 $(M+H)^+$	154—156 Et_2O–Hex
10g	2.50—2.80 (2H, m), 3.76 (1H, m), 4.40 (1H, dd, J=4.5, 17.5 Hz), 4.59 (1H, m), 4.70 (1H, d, J=17.5H), 5.74 (2H, br), 6.72 (1H, m), 6.96 (1H, m), 7.02—7.13 (3H, m), 7.20—7.34 (4H, m), 7.43—7.56 (4H, m), 7.64—7.73 (3H, m)	A	588 $(M+H)^+$	Amorphous Solid
10h	1.94 (3H, s), 1.99 (3H, s), 2.37 (3H, s), 2.53—2.90 (2H, m), 3.80 (1H, m), 4.39 (1H, d, J= 17 Hz), 4.57—4.96 (2H, m), 6.72 (1H, d, J=7.5 Hz), 6.87 (1H, d, J=8.5 Hz), 6.92—7.17 (5H, m), 7.27 (1H, s), 7.29 (2H, d, J=8.5 Hz), 7.32—7.60 (3H, m), 8.21 (1H, m)	A	562 $(M+H)^+$	Amorphous Solid
10i	1.98 (3H, s), 2.01 (3H, s), 2.62 (1H, m), 2.75 (1H, m), 3.82 (1H, m), 4.32 (1H, d, J=16 Hz), 4.68 (1H, m), 4.86 (1H, d, J=16 Hz), 6.74 (1H, m), 6.86 (2H, d, J=8 Hz), 6.97 (1H, m), 7.07 (2H, d, J=8 Hz), 7.14 (1H, d, J=8 Hz), 7.18—7.37 (5H, m), 7.45—7.65 (3H, m), 8.24 (1H, d, J=8 Hz)	A	548 $(M+H)^+$	168—170 Et_2O

a) A, $CDCl_3$; B, DMSO-d_6. *b*) Recrystallization solvent: IPE, diisopropyl ether; Hex, hexane.

Table 7. Spectral and Physical Data for Compounds **8c—f, h, 14c—f** and **14h**

Compd. No.	^{1}H-NMR($CDCl_3$), δ (ppm)	FAB-MS *m/z*	mp (°C) Solvent[a)]
8c	2.07 (3H, s), 7.07 (1H, m), 7.12—7.32 (4H, m), 7.41 (1H, dd, *J*=8, 8 Hz), 7.56 (1H, dd, *J*=8, 8 Hz), 8.02 (1H, d, *J*=8Hz)	213 $(M+H)^+$	93—95 Et_2O–Hex
8d	2.04 (3H, s), 2.37 (3H, s), 6.93—7.08 (3H, m), 7.22 (1H, m), 7.41 (1H, m), 7.56 (1H, m), 8.02 (1H, m)	227 $(M+H)^+$	129—130 Et_2O–Hex
8e	2.37 (3H, s), 7.07 (1H, m), 7.10—7.38 (4H, m), 7.40 (1H, dd, *J*=8, 8 Hz), 7.55 (1H, dd, *J*=8, 8 Hz), 8.01 (1H, d, *J*=8 Hz)	213 $(M+H)^+$	95—97 IPE-Hex
8f	7.15—7.32 (2H, m), 7.48—7.63 (4H, m), 7.70 (1H, d, *J*=8 Hz), 8.08 (1H, d, *J*=8 Hz)	267 $(M+H)^+$	135—136 IPE-Hex
8h	1.92 (6H, s), 7.00—7.22 (4H, m), 7.44 (1H, dd, *J*=8, 8 Hz), 7.61 (1H, dd, *J*=8, 8 Hz), 8.10 (1H, d, *J*=8 Hz)	227 $(M+H)^+$	145—146 Et_2O–Hex
14c	1.20 (6H, s), 2.11 (3H, s), 3.65 (1H, d, *J*=7 Hz), 3.71 (1H, d, *J*=7 Hz), 7.09—7.30 (5H, m), 7.31—7.41 (1H, m), 7.41—7.53 (1H, m), 7.80 (1H, dd, *J*=8, 2 Hz)	266 $(M+H)^+$	Amorphous Solid
14d	1.21 (6H, s), 2.10 (3H, s), 2.36 (3H, s), 3.70 (2H, m), 6.93—7.08 (3H, m), 7.21 (1H, d, *J*=8 Hz), 7.34 (1H, dd, *J*=8, 8 Hz), 7.46 (1H, dd, *J*=8, 8 Hz), 7.78 (1H, d, *J*=8 Hz)	280 $(M+H)^+$	Amorphous Solid
14e	1.20 (6H, s), 2.41 (3H, s), 3.65 (2H, m), 7.09—7.30 (5H, m), 7.31—7.41 (1H, m), 7.41—7.53 (1H, m), 7.80 (1H, dd, *J*=8, 2 Hz)	266 $(M+H)^+$	Amorphous Solid
14f	1.15 (3H, s), 1.20 (3H, s), 3.59 (1H,d, *J*=7 Hz), 3.72 (1H, d, *J*=7 Hz), 7.25 (1H, d, *J*=8 Hz), 7.37—7.57 (5H, m), 7.69 (1H, d, *J*=8 Hz), 7.90 (1H, m)	320 $(M+H)^+$	Oil
14h	1.16 (6H, s), 1.98 (6H, s), 3.62 (2H, s), 6.99—7.21 (4H, m), 7.37 (1H, dd, *J*=8, 8 Hz), 7.49 (1H, dd, *J*=8, 8 Hz), 7.80 (1H, d)	280 $(M+H)^+$	Oil

a) Recrystallization solvent: IPE, diisopropyl ether; Hex, hexane.

Table 8. Analytical and Spectral Data for Compounds **11a—h**

Compd. No.	^{1}H-NMR($CDCl_3$), δ (ppm)	FAB-MS *m/z*	mp (°C) Solvent[a)]	Formula	Calcd (Found)		
					C	H	N
11a	2.35 (3H, s), 2.40—2.70 (5H, m), 2.75—2.95 (1H, m), 3.55—3.90 (5H, m), 4.08 (1H, d, *J*=8 Hz), 4.70 (1H, dt, *J*=5, 14 Hz), 5.15 (1H, d, *J*=16 Hz), 6.70 (1H, d, *J*=8 Hz), 6.95 (4H, d, *J*=10 Hz), 7.08 (2H, d, *J*=8 Hz), 7.18—7.60 (9H, m), 7.83 (1H, dd, *J*=2, 8 Hz)	602 $(M+H)^+$	147—150 AcOEt–Hex	$C_{36}H_{35}N_5O_4$	71.86 (71.72	5.86 5.97	11.64 11.62)
11b	2.35 (3H, s), 2.39 (3H, s), 2.40—2.95 (6H, m), 3.55—3.90 (5H, m), 4.10 (1H, d, *J*=16 Hz), 4.71 (1H, dt, *J*=5, 10 Hz), 5.18 (1H, d, *J*=16 Hz), 6.72 (1H, d, *J*=8 Hz), 6.88—7.60 (14H, m), 7.80 (1H, dd, *J*=1, 8 Hz)	616 $(M+H)^+$	161—163 EtOH–H_2O	$C_{37}H_{37}N_5O_4$	72.17 (72.09	6.06 6.21	11.37 11.22)
11c	2.07 and 2.10 (total 3H, s), 2.38 (3H, s), 2.40—2.68 (4H, m), 2.72—2.95 (1H, m), 3.56—3.88 (6H, m), 4.09 (1H, dd, *J*=1, 15 Hz), 4.60—4.80 (1H, m), 5.18 (1H, dd, *J*=1, 15 Hz), 6.65—6.75 (1H, br), 6.82—7.00 (3H, m), 7.06 (2H, d, *J*=8 Hz), 7.17—7.40 (7H, m), 7.53 (2H, ddt, *J*=1, 9, 15 Hz), 8.10 (1H, d, *J*=7 Hz)	616 $(M+H)^+$	150—154 AcOEt–Hex	$C_{37}H_{37}N_5O_4$	72.17 (72.09	6.06 6.21	11.37 11.22)
11d	1.97 and 2.01 (total 3H, s), 2.33 (3H, s), 2.38 (3H, s), 2.42—2.56 (5H, m), 2.81 (1H, m), 3.56—3.87 (5H, m), 4.05 (1H, d, *J*=18 Hz), 4.71 (1H, m), 5.69 (1H, d, *J*=18 Hz), 6.69 (1H, br), 6.85 (1H, d, *J*=9 Hz), 6.93 (1H, m), 7.02—7.26 (8H, m), 7.36 (1H, dd, *J*=1, 8 Hz), 7.44—7.60 (2H, m), 8.06 (1H, d, *J*=8 Hz)	630 $(M+H)^+$	160—162 AcOEt–Hex	$C_{38}H_{39}N_5O_4$	72.47 (72.31	6.24 6.38	11.12 11.02)
11e	2.29 (3H, s), 2.36 (3H, s), 2.41—2.67 (5H, m), 2.82 (1H, m), 3.56—3.87 (5H, m), 4.07 (1H, d, *J*=16 Hz), 4.71 (1H, dt, *J*=5, 13 Hz), 5.70 (1H, d, *J*=16 Hz), 6.69 (1H, d, *J*=7.5 Hz), 6.88—7.00 (3H, m), 7.08 (2H, d, *J*=8.5 Hz), 7.17—7.58 (10H, m), 7.86 (1H, m)	616 $(M+H)^+$	150—153 Et_2O	$C_{37}H_{37}N_5O_4$	72.17 (72.03	6.06 6.18	11.37 11.26)
11f	2.37 (3H, s), 2.40—2.66 (5H, m), 2.82 (1H, m), 3.58 (2H, m), 3.70 (2H, m), 3.77 (1H, m), 4.05 (1H, d, *J*=16 Hz), 4.70 (1H, m), 5.69 (1H, d, *J*=16 Hz), 6.70 (1H, d, *J*=7.5 Hz), 6.93 (1H, t, *J*=7.5 Hz), 7.00—7.11 (4H, m), 7.15—7.36 (5H, m), 7.43—7.60 (4H, m), 7.73—7.81 (2H, m)	670 $(M+H)^+$	160—161 AcOEt–Hex	$C_{37}H_{34}F_3N_5O_4$	66.36 (66.21	5.12 5.29	10.46[b)] 10.18)
11g	1.92 (3H, s), 1.99 (3H, s), 2.36 (3H, s), 2.40 (3H, s), 2.42—2.67 (4H, m), 2.83 (1H, m), 3.59 (2H, m), 3.72 (2H, m), 3.80 (1H, m), 4.04 (1H, d, *J*=17 Hz), 4.70 (1H, m), 5.20 (1H, d, *J*=17 Hz), 6.69 (1H, d, *J*=7.5 Hz), 6.75 (2H, d, *J*=8.5 Hz), 6.92 (1H, m), 7.02—7.23 (5H, m), 7.34 (1H, dd, *J*=1.5, 7.5 Hz), 7.44—7.60 (3H, m), 8.25 (1H, dd, *J*=1.5, 7.5 Hz)	644 $(M+H)^+$	157—158 EtOH–H_2O	$C_{39}H_{41}N_5O^4$	72.76 (72.53	6.42 6.49	10.88 10.72)
11h	1.99 (3H, s), 2.04 (3H, s), 2.36 (3H, s), 2.43—2.68 (5H, m), 2.81 (1H, m), 3.56—3.86 (5H, m), 4.05 (1H, d, *J*=16 Hz), 4.69 (1H, m), 5.18 (1H, d, *J*=16 Hz), 6.69 (1H, d, *J*=7.5 Hz), 6.82—6.96 (3H, m), 7.07 (2H, d, *J*=8.5 Hz), 7.12—7.37 (7H, m), 7.44—7.64 (2H, m), 8.28 (1H, dd, *J*=1.5, 7.5 Hz)	630 $(M+H)^+$	185—188 AcOEt–Hex	$C_{38}H_{39}N_5O_4$	72.47 (72.26	6.24 6.49	11.12 11.15)

a) Recrystallization solvent: Hex, hexane. *b*) Calcd (Found): F, 8.51 (8.47).

29 mmol). The mixture was stirred at 80 °C for 0.5 h and added to a solution of 1-[4,4-dimethyl-(2,5-oxazolinyl)]-2-methoxybenzene (**13**)[23] (3.0 g, 14.6 mmol) in tetrahydrofuran (20 ml) at room temperature. The mixture was stirred at 40 °C for 5 h. The solvent was concentrated and the residue was poured into saturated aqueous ammonium chloride (40 ml) and extracted with AcOEt. The organic layer was washed with water and brine, dried over magnesium sulfate, filtered, and concentrated to give the crude product. The crude product was purified by column chromatography on silica gel (0.1% MeOH in $CHCl_3$) to give **14c** (5.0 g, 65%) as a white solid. ^{1}H-NMR ($CDCl_3$) δ: 1.20 (6H, s), 2.11 (3H, s), 3.65 (1H, d, J=7 Hz), 3.71 (1H, d, J=7 Hz), 7.09—7.30 (5H, m), 7.31—7.41 (1H, m), 7.41—7.53 (1H, m), 7.80 (1H, dd, J=8, 2 Hz). FAB-MS m/z: 266 $(M+H)^+$.

Compounds **14d—f** and **14h** were synthesized in the same manner as described for **14c**.

Spectral data are summarized in Table 7.

2-(2-Methylphenyl)benzoic Acid (8c) A solution of **14c** (5.0 g, 18.9 mmol) in 60 ml of 6 N HCl was refluxed for 60 h. After cooling to room temperature, the mixture was extracted with ether. The organic layer was washed with water, dried ($MgSO_4$) and concentrated to give the crude solid. The solid was recrystallized from diethyl ether–hexane (1 : 1) to give **8c** as pale yellow crystals (2.0 g, 50%), mp 93—95 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.07 (3H, s), 7.07 (1H, m), 7.12—7.32 (4H, m), 7.41 (1H, dd, J=8, 8 Hz), 7.56 (1H, dd, J=8, 8 Hz), 8.02 (1H, d, J=8 Hz). FAB-MS m/z: 213 $(M+H)^+$.

Compounds **8d—f** and **8h** were synthesized in the same manner as described for **8c**.

Spectral data are summarized in Table 7.

***N*-[4-[[2,6-Diaza-6-[2-(4-(dimethylamino)piperidyl)-2-oxoethyl]-5-oxobicyclo[5.4.0]undeca-1(11),7(8),9-trien-2-yl]carbonyl]phenyl][2-(4-methylphenyl)phenyl]formamide (15)** The title compound was prepared in a similar manner to that described for **11b**, using *N*,*N*-dimethylaminopiperidine, instead of *N*-methylpiperazine. Slight yellow crystals, mp 198—199 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.42—1.73 (2H, m), 1.80—2.11 (2H, m), 2.28—2.50 (1H, m), 2.30 (6H, s), 2.38 (3H, s), 2.56—2.93 (3H, m), 3.05—3.30 (1H, m), 3.82 (1H, dd, J=13, 5 Hz), 3.90—4.19 (2H, m), 4.58—4.80 (2H, m), 5.21 (1H, dd, J=16, 10 Hz), 6.70 (1H, d, J=9 Hz), 6.89—7.04 (4H, m), 7.09 (2H, d, J=8 Hz), 7.15—7.60 (8H, m), 7.83 (1H, dd, J=8, 1 Hz). *Anal.* Calcd for $C_{39}H_{41}N_5O_4$: C, 72.76; H, 6.42; N, 10.88. Found: C, 72.65; H, 6.56; N, 10.78.

2-[2,6-Diaza-6-[[4-[[2-(4-methylphenyl)phenyl]carbonylamino]-phenyl]carbonyl]-3-oxobicyclo[5.4.0]undeca-1(7),8,10-trien-2-yl]-*N*-[2-(dimethylamino)ethyl]ethanamide (16) The title compound was prepared in a similar manner to that described for **11b**. White crystals, mp 136—139 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.20 (6H, s), 2.32—2.41 (2H, m), 2.36 (3H, s), 2.55—2.86 (2H, m), 3.23—3.41 (2H, m), 3.83 (1H, dd, J=13, 5 Hz), 4.22 (1H, d, J=15 Hz), 4.60—4.72 (1H, m), 4.70 (1H, d, J=15 Hz), 6.72 (1H, d, J=9 Hz), 6.80—6.89 (1H, br), 6.92—7.03 (4H, m), 7.08 (2H, d, J=9 Hz), 7.16—7.25 (2H, m), 7.26—7.59 (5H, m), 7.82 (1H, dd, J=7, 1 Hz). *Anal.* Calcd for $C_{36}H_{37}N_5O_4$: C, 71.62; H, 6.18; N, 11.60. Found: C, 71.71; H, 6.09; N, 11.82.

2-[2,6-Diaza-6-[[4-[[2-(4-methylphenyl)phenyl]carbonylamino]-phenyl]-carbonyl]-3-oxobicyclo[5.4.0]undeca-1(7),8,10-trien-2-yl]-*N*-(dimethyl-amino)ethanamide (17) The title compound was prepared in a similar manner to that described for **11b**. White crystals, mp 177—181 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.38 and 2.39 (total 3H, s), 2.55 and 2.65 (total 6H, s), 2.66—2.90 (2H, m), 3.82 (1H, dd, J=13, 6 Hz), 4.15 (1H, d, J=17 Hz), 4.54—4.81 (2H, m), 5.36 (1H, d, J=17 Hz), 6.35 (1H, s), 6.71 (1H, d, J=8 Hz), 6.90—7.59 (14H, m), 7.82 (1H, dd, J=8, 1 Hz). *Anal.* Calcd for $C_{34}H_{33}N_5O_4$: C, 70.94; H, 5.78; N, 12.17. Found: C, 70.74; H, 5.89; N, 11.99.

2-[2,6-Diaza-6-[[4-[[2-(4-methylphenyl)phenyl]carbonylamino]-phenyl]-carbonyl]-3-oxobicyclo[5.4.0]undeca-1(7),8,10-trien-2-yl]-*N*-(4-methylpiperazinyl)ethanamide (18) The title compound was prepared in a similar manner to that described for **11b**. White crystals, mp 161—165 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.30 and 2.32 (total 3H, s), 2.38 and 2.39 (total 3H, s), 2.52—2.91 (8H, m), 3.04—3.08 (2H, m), 3.82 (1H, dd, J=12, 5 Hz), 4.09 (1H, d, J=17 Hz), 4.60—4.80 (1H, m), 5.37 (1H, d, J=17 Hz), 6.38—6.41 (1H, brs), 6.68—6.76 (1H, m), 6.90—7.07 (4H, m), 7.08—7.61 (10H, m), 7.82 (1H, dd, J=8, 1 Hz). *Anal.* Calcd for $C_{37}H_{38}N_6O_4$: C, 70.46; H, 6.07; N, 13.32. Found: C, 70.35; H, 6.29; N, 13.20.

2-[2,6-Diaza-6-[[4-[[2-(4-methylphenyl)phenyl]carbonylamino]-phenyl]-carbonyl]-3-oxobicyclo[5.4.0]undeca-1(7),8,10-trien-2-yl]-*N*-morpholin-4-ylethanamide (19) The title compound was prepared in a similar manner to that described for **11b**. White crystals, mp 187—190 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.37 and 2.38 (total 3H, s), 2.53—2.92 (5H, m), 3.00—3.33 (1H, m), 3.72—3.95 (4H, m), 4.13 (1H, d, J=17 Hz), 4.58—4.80 (2H, m), 5.37 (1H, d, J=17 Hz), 6.48 (1H, s), 6.68—6.78 (1H, br), 6.90—7.09 (4H, m), 7.10—7.60 (10H, m), 7.82 (1H, dd, J=8, 1 Hz). *Anal.* Calcd for $C_{36}H_{35}N_5O_5$: C, 70.00; H, 5.71; N, 11.34. Found: C, 69.86; H, 5.88; N, 11.26.

2-(Dimethylamino)ethyl 2-[2,6-diaza-6-[[4-[[2-(4-methyl-phenyl)-phenyl]carbonylamino]phenyl]carbonyl]-3-oxobicyclo[5.4.0]undeca-1(11),7(8),9-trien-2-yl]acetate (20) The title compound was prepared in a similar manner to that described for **11b**, using *N*,*N*-dimethylaminoethanol instead of *N*-methylpiperazine. White crystals, mp 142—145 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.32 (6H, s), 2.37 (3H, s), 2.56—2.81 (2H, m), 2.63 (2H, t, J=5 Hz), 3.83 (1H, dd, J=11, 5 Hz), 4.25 (1H, d, J=18 Hz), 4.34 (2H, t, J=5 Hz), 4.61—4.80 (1H, m), 4.89 (1H, d, J=18 Hz), 6.74 (1H, d, J=8 Hz), 6.96 (4H, d, J=9 Hz), 7.10 (2H, d, J=8 Hz), 7.16—7.36 (5H, m), 7.38—7.59 (3H, m), 7.83 (1H, dd, J=8, 1 Hz). *Anal.* Calcd for $C_{36}H_{36}N_4O_5$: C, 71.50; H, 6.00; N, 9.27. Found: C, 71.34; H, 6.22; N, 9.21.

2,6-Diaza-2-[3-(dimethylamino)ethyl]-6-[(4-nitrophenyl)carbonyl]- bicyclo[5.4.0]undeca-1(11),7(8),9-trien-3-one (21a) The title compound was prepared in a similar manner to that described for **6**. Slightly yellow crystals, mp 128—131 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.26 (6H, s), 2.58—2.83 (4H, m), 3.80—4.00 (2H, m), 4.08—4.24 (1H, m), 4.78 (1H, ddd, J=5, 13, 13 Hz), 6.65 (1H, d, J=8 Hz), 6.91 (1H, dd, J=1, 8 Hz), 7.25—7.35 (1H, m), 7.43 (1H, dd, J=1, 8 Hz), 7.63 (2H, d, J=9 Hz), 8.02 (1H, d, J=9 Hz). FAB-MS m/z: 383 $(M+H)^+$.

2,6-Diaza-2-[3-(dimethylamino)propyl]-6-[(4-nitrophenyl)carbonyl]-bicyclo[5.4.0]undeca-1(11),7(8),9-trien-3-one (21b) The title compound was prepared in a similar manner to that described for **6**. White amorphous solid, ^{1}H-NMR ($CDCl_3$) δ: 1.88—2.10 (3H, m), 2.27 (6H, s), 2.43 (2H, d, J=7 Hz), 2.57—2.86 (2H, m), 3.78—3.90 (2H, m), 3.98 (2H, t, J=7 Hz), 4.78 (1H, m), 6.67 (1H, d, J=8 Hz), 6.93 (1H, t, J=8 Hz), 7.25—7.42 (4H, m), 8.03 (2H, d, J=9 Hz). FAB-MS m/z: 397 $(M+H)^+$.

6-[(4-Aminophenyl)carbonyl]-2,6-diaza-2-[3-(dimethylamino)ethyl]-bicyclo[5.4.0]undeca-1(11),7(8),9-trien-3-one (22a) The title compound was prepared in a similar manner to that described for **7**. Brown amorphous solid, ^{1}H-NMR ($CDCl_3$) δ: 2.39 (6H, s), 2.50—2.75 (4H, m), 3.77—3.90 (3H, br), 3.92—4.15 (2H, m), 4.56—4.78 (1H, m), 6.40 (1H, d, J=9 Hz), 6.79 (1H, d, J=9 Hz), 6.99 (1H, dt, J=1, 8 Hz), 7.12—7.26 (1H, m), 7.15 (1H, d, J=9 Hz), 7.29 (1H, dd, J=1, 8 Hz), 7.42 (1H, dd, J=1, 8 Hz). FAB-MS m/z: 353 $(M+H)^+$.

6-[(4-Aminophenyl)carbonyl]-2,6-diaza-2-[3-(dimethyl-amino)-propyl]-bicyclo[5.4.0]undeca-1(11),7(8),9-trien-3-one (22b) The title compound was prepared in a similar manner to that described for **7**. White amorphous solid, ^{1}H-NMR ($CDCl_3$) δ: 1.87—2.03 (3H, m), 2.23 (6H, s), 2.35—2.46 (2H, m), 2.51—2.64 (2H, m), 3.35—3.89 (3H, m), 4.03 (1H, m), 4.65 (1H, m), 6.40 (2H, d, J=9 Hz), 6.79 (1H, d, J=8 Hz), 6.98 (1H, ddd, J=8, 8, 1 Hz), 7.07 (2H, d, J=9 Hz), 7.20—7.35 (2H, m). FAB-MS m/z: 367 $(M+H)^+$.

***N*-[4-[[2,6-Diaza-6-[2-[(dimethylamino)ethyl]-5-oxobicyclo[5.4.0]-undeca-1(11),7(8),9-trien-2-yl]carbonyl]phenyl][2-(4-methylphenyl)-phenyl]formamide (23a)** The title compound was prepared in a similar manner to that described for **9b**. White prisms, mp 178—181 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.29 (6H, s), 2.36 (3H, s), 2.50—2.75 (4H, m), 3.80 (1H, dd, J=5, 13 Hz), 3.90—4.19 (2H, m), 4.68 (1H, dt, J=5, 13 Hz), 6.70 (1H, d, J=7 Hz), 6.90—7.12 (4H, br s), 7.18—7.60 (10H, m), 7.85 (1H, d, J=7 Hz). *Anal.* Calcd for $C_{34}H_{34}N_4O_3$: C, 74.70; H, 6.27; N, 10.25. Found: C, 74.62; H, 6.40; N, 10.21.

***N*-[4-[[2,6-Diaza-6-[3-[(dimethylamino)propyl]-5-oxobicyclo[5.4.0]-undeca-1(11),7(8),9-trien-2-yl]carbonyl]phenyl][2-(4-methylphenyl)-phenyl]formamide (23b)** The title compound was prepared in a similar manner to that described for **9b**. White crystals, mp 155—158 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.86—2.05 (2H, m), 2.23 (6H, s), 2.37 (3H, s), 2.37—2.42 (2H, m), 2.50—2.76 (2H, m), 3.23—4.02 (3H, m), 4.57 (1H, m), 6.72 (1H, br), 6.90—7.02 (3H, m), 7.02—7.56 (13H, m), 7.84 (1H, dd, J=1.5, 7.5 Hz). *Anal.* Calcd for $C_{35}H_{36}N_4O_3$: C, 74.98; H, 6.47; N, 9.99. Found: C, 74.87; H, 6.49; N, 9.95.

***In Vitro* Receptor Binding Assays**[7a,9] Membrane suspensions were prepared from Sprague–Dawley male rat liver and kidney (medullopapillary regions) for V_1 and V_2 receptor binding, respectively. Competitive binding experiments were conducted at equilibrium (V_1, 1 h; V_2, 2 h at 25 °C), using 0.5 nM [^{3}H]-vasopressin in the presence of various concentrations of test compounds. Nonspecific binding was determined with 1 mM [d(CH_2)$_5$, Tyr^2(Me), Arg^8]-vasopressin for the V_1 receptor, and [d(CH_2)$_5$, D-Ile^2, Ile^4, Arg^8]-vasopressin for the V_2 receptor.

Aquaretic Effects of Orally Administered Compound 11b to Normal

Conscious Rats Adult, male Sprague–Dawley rats weighing 175 to 195 g were deprived of food for 24 h but allowed free access to water. Rats were orally dosed with vehicle (0.5% methylcellulose, 5 ml/kg) or compound **11b** at doses of 1 to 10 mg/kg and then placed in a group of three in a metabolic cage. During experiments, the rats received water and food *ad libitum*. Spontaneously voided urine was collected every 3 h for 6 h period. Urine osmolarity was measured using the freezing point depression method.

Antagonism to AVP Induced Antidiuretic Action (i.v.) Adult, male Sprague–Dawley rats weighing 200 to 230 g were used in this experiment. Rats were anesthetized with ether, and then both femoral vein and bladder were cannulated for i.v. injection and urine collection, respectively. After recovery from anesthesia (3 h), rats were given a constant infusion of 0.3% NaCl solution through a cannula in the right femoral vein. Urine was collected every 10 min for a 40 min period, and then the 0.3% NaCl solution was changed to vasopressin-containing solution (0.1 mU/kg/min). After 40 min, vehicle or compound **11b** was intravenously administered at doses of 0.1 and 0.32 mg/kg.

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