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1,3-Disubstituted Benzazepines as Neuropeptide Y Y1 Receptor Antagonists

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Abstract—A novel class of potent and selective non-peptide neuropeptide Y (NPY) Y1 receptor antagonists, having benzazepine nuclei, have been designed, synthesized, and evaluated for activity. Through a blind screening we found the compound 1-*N*-(3-(*N*′-(*tert*-butoxycarbonyl)amino)benzyl)-7-methoxy-(3-(3)-methylureido)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (**9**: $IC_{50} = 1.6$ μM). Chemical modifications of **9** gave a potent NPY Y1 antagonist 3-(*N*-(4-hydroxyphenyl)-*N*′-methylguanidino)-1-*N*-(3-(*N*′-(*tert*-butoxycarbonyl)amino)benzyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (**14c**: $IC_{50} = 43$ nM), which had no affinity for NPY Y2 and Y5 receptors.

Introduction

Neuropeptide Y (NPY), a 36-amino acid polypeptide hormone was discovered in 1982 by Tatemoto et al.[1] NPY is suggested to play diverse physiological roles in the control of cardiovascular function,[2] food intake,[3] energy production, pain,[4] and anxiety via a number of G-protein coupled receptors,[5–8] Y1,[9] Y2,[10] Y4/PP1,[11] and Y5.[3] Of the receptors, the Y1 receptor is best characterized and has been demonstrated to mediate long-lasting vasoconstriction in the periphery.[12] On the other hand, the Y1 receptor in the central nervous system appears to participate in food intake because a selective Y1 antagonist inhibits the increase in food intake after intracerebroventricular injection of NPY.[13] The recently cloned Y5 receptor is also suggested to be involved in feeding behavior,[3] but further investigation is needed to prove this suggestion. These observations revealed that the NPY Y1 receptor may be very useful for targeted therapeutic treatment, especially for congestive heart failure, angina pectoris, hypertension, and obesity.

To date, four non-peptide NPY Y1 receptor antagonists, BIBP3226 ($K_i = 7.2$ nmol),[13] SR120819A ($K_i = 15$ nmol),[14] PD160170 ($K_i = 48$ nmol),[15] and LY-357897 ($K_i = 0.75$ nmol),[16] have been reported. In the course of our screening of the Shionogi compound library, we found compound **9** which showed μmol order of binding affinity for the NPY Y1 receptor. Compound **9** has a benzazepine nucleus, which prompted us to pursue its chemical modification. In this paper, we report the design, synthesis and discovery of a series of novel potent and selective NPY Y1 receptor antagonists, compound **1** (Fig. 1).

Chemistry

3-Aminobenzylalcohol, **2**, was treated with $(BOC)_2O$ to protect the amino group and then brominated with NBS and triphenylphosphine to give a benzyl bromide derivative, **4** (Scheme 1). *N*-Alkylation of 3-azidobenzazepine, **7b**,[17] or 3-azido-7-methoxybenzazepine, **7a**, which was prepared from 7-methoxybenzazepine, **5**,[18] by the same procedure described for the preparation of **7b**,[17] was achieved by reaction with **4** under phase transfer conditions (Method A) and then the azide group was reduced to amino compounds **8a** and **8b**. Urea derivatives, **9** and **10a–s**, were prepared by several methods as outlined in Scheme 2. First, an amino compound, **8a** or **8b**, was treated with isocyanates to obtain urea derivatives **9** and **10a–f** (Method B). Second, **8b** was treated with carbonyldiimidazole and then with amines to obtain **10g** (Method C1). Alternatively, carbonyldiimidazole and several protected amines were reacted initially to give imidazolylaminocarbonyl compound which was then reacted with **8b**, followed by deprotection to

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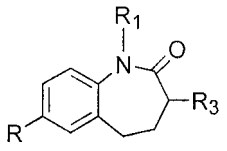

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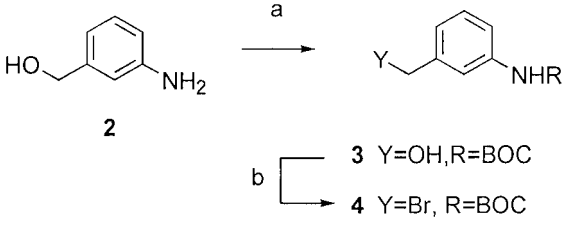
Figure 1. Substitutents R, R_1, and R_3 selected for chemical modifications.

give ureas **10i** and **10j** (Method C2). Third, **8b** was treated with triphosgene and triethylamine, followed by the reaction with amines to give ureas (**10h, 10l, 10n, 10o, 10p, 10r**, and **10s**) (Method D). In a synthesis of **10q, 8b** was reacted with the isocyanate which was generated in situ according to Method D from 5-amino-1-tosyl-benzimidazole prepared from 5-nitro-1-tosyl-benzimidazole[19] by catalytic hydrogenolysis and then hydrolyzed by treatment with methanolic KOH. Compound **10k** was obtained by the treatment of **8b** with 4-phenoxycarbonylaminobenzoic acid[20] (Method E). Compound **10j** was converted to **10m** by the treatment with sulfur trioxide pyridine complex, followed by treatment with aqueous NaOH.

7b was converted to compound **11a–n** by the same procedure described for the preparation of **10a** (Scheme 3).

8b was converted to an amide, **12**, and a carbonate derivative, **13**, by treatment with acetyl chloride and methylchlorocarbonate, respectively. **8b** was further converted to guanidine derivatives, **14a–c**, by the reaction with *S*-methylisothiourea hydroiodide salt, or **14d–g** by the reaction with isothiocyanate compounds, followed by methylation at the sulfur position with methyliodide and then by heating with amines, as shown in Scheme 4.

3-(Phthalimido)-2,3-dihydro-1,5(5*H*)-benzothiazepine-4-one, **15**,[21] was treated with hydrazine hydrate and then with phenylisocyanate to give an urea derivative, which was *N*-alkylated as above to afford **16**. 3-(Cbz-amino)-2,3-dihydro-1,5(5*H*)-benzoxazepine-4-one, **17**,[21] was *N*-alkylated as above and after removal of the Cbz group by hydrogenolysis, the amino compound was converted to the urea derivative, **18** (Schemes 5 and 6).



Scheme 1. *Reagents:* (a) $(BOC)_2O$; (b) NBS, PPh_3, CH_2Cl_2.

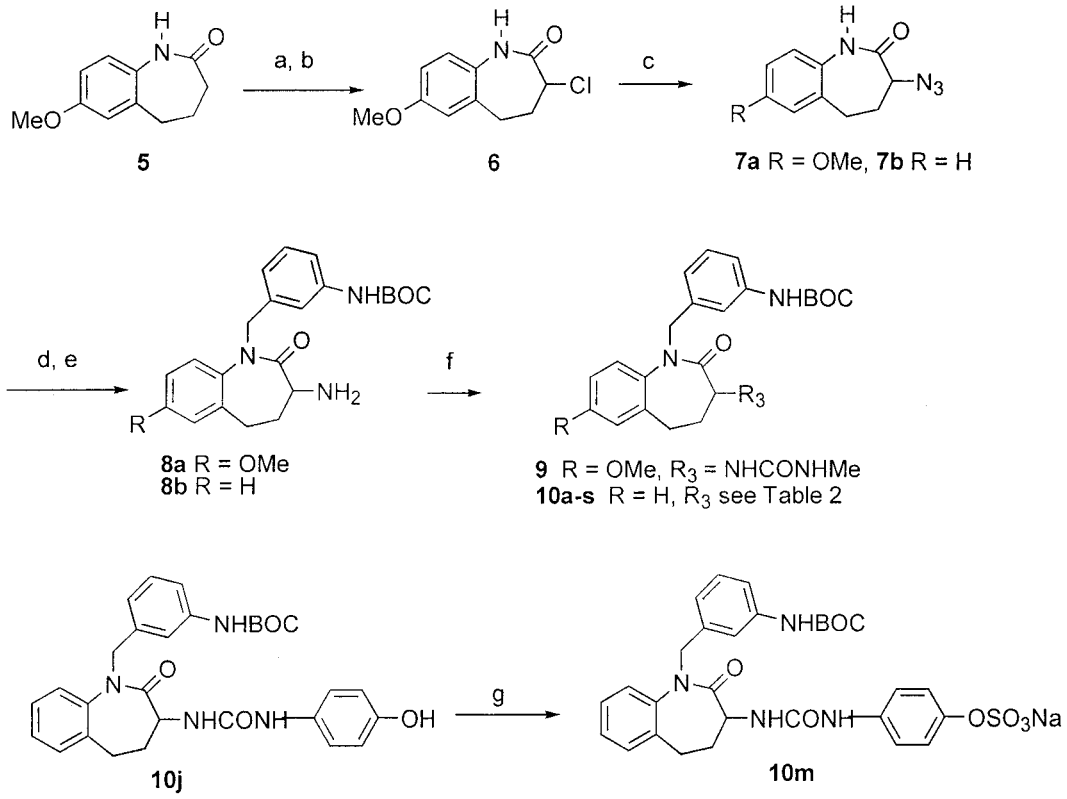
Structure–Activity Relationship and Discussion

The compounds prepared in this study were evaluated as NPY Y1 antagonists by testing their potency to displace [^{125}I]peptide YY ([^{125}I]PYY) binding to SK-N-MC cells. To find antagonists more active than **9**, which was found to be active by a blind screening, three positions for substituents, R, R_1, and R_3 of **1**, were selected for chemical modification.

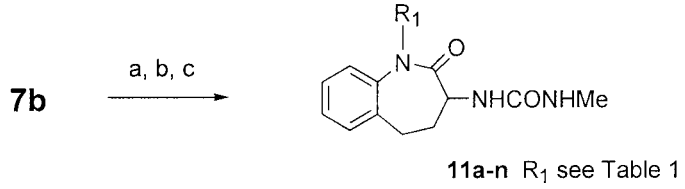
We first evaluated whether the OMe group at position 6 was indispensable for the activity of the NPY Y1 binding affinity. Since the OMe group deficient analogue **10a** had slightly stronger binding affinity than **9**, we carried out the chemical modification on unsubstituted compounds at the benzene ring. When substituent R_3 was fixed to the 3-methyl ureido group, we introduced various kinds of bulky alkyl groups to R_1, but none of them were active (Table 1). Therefore, the variation of R_3 was examined when substituent R_1 was fixed as the 3-*N*-(*tert*-butoxycarbonylamino)benzyl group (Table 2). As the bulkiness of the alkyl group at the urea moiety increases, the binding affinity decreased (**10a–d**). The absence of hydrogen of the terminal urea eliminated binding affinity (**10g** versus **10a** and **10b**). This suggests that the ureido hydrogen interacts with a hydrogen bond acceptor in the binding site of the NPY Y1 receptor. The compounds with aryl groups at the 3-position of the urea group were more potent than **10a**. The fact that the phenyl urea group, but not the cyclohexyl one, enhanced binding affinity (**10d** versus **10e**) indicates that the aromaticity of the substituents at urea is favorable for the NPY Y1 binding affinity. The effects of introducing a substituent to the *ortho*-, *meta*-, or *para*-position of the ureido benzene ring were examined next (**10h, 10i,** and **10j**). The *para*-substituted one **10j** was the most potent and thus was chosen for further modification. Because the phenolic proton was acidic, we introduced an acidic group such as a carboxyl group and a tetrazolyl group at the *para*-position (**10k, 10l** and **10m**) but they were detrimental to the activity. We also examined the effect of introducing heteroaromatic groups. Basic groups, such as pyridine or pyrimidine groups, had an unfavorable effect on the receptor binding affinity (**10n** and **10o**), and the *tert*-Bu group may be too bulky a substituent (**10q**). The *tert*-Bu group may cause an unfavorable steric interation with the receptor. Only the compound **10s** was more potent than **10e**.

Replacement of the urea with amide or carbonate moiety resulted in two and fourfold decrease in affinity (**12** and **13** versus **10a**). However, replacement of the urea with monosubstituted guanidine moiety (**14a-c**) gave a 2.7–8.4 times more potent compound than the corresponding urea compound. The *N*-methylated compound **14d** was 2.8-fold more potent than **14c** and was 10.7-fold more potent than **10e**, but other *N*-disubstituted guanidine and *N*-trisubstituted ones (**14f–g**) lost the binding affinity (Table 3).

Other modifications were examined, such as introduction of hetero atoms in the lactam ring (**16, 18**). Compound **16**, having a benzothiazepine nuclei, was as potent as



Scheme 2. *Reagents:* (a) PCl_5; (b) H_2, 5% Pd-C, MeOH; (c) NaN_3, DMF; (d) Method A: **4**, KOH, $Bu_4N^+Br^-$, THF; (e) H_2, 10% Pd-C, MeOH; (f) Method B: $R_3'NCO$; Method C1: (i) Imd_2CO, CH_3CN; (ii) amines; Method C2: (i) Imd_2CO, amines, THF; (ii) deprotection; Method D: $(CCl_3O)_2CO$, TEA, amines, CH_2Cl_2; or Method E: 4-phenoxycarbonylaminobenzoic acid, DMF. (g) (i) SO_3 + pyr, pyridine; (ii) NaOH aq.



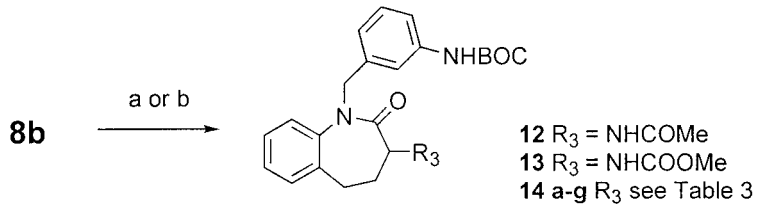
Scheme 3. *Reagents:* (a) H_2, 10% Pd-C; (b) MeNCO; (c) R_1X (X = Cl, Br, or I) (Method A).

the parent compound **10e**, but compound **18**, having a benzoxazepine nuclei, dramatically reduced NPY Y1 binding affinity compared to compound **10e** (Table 4).

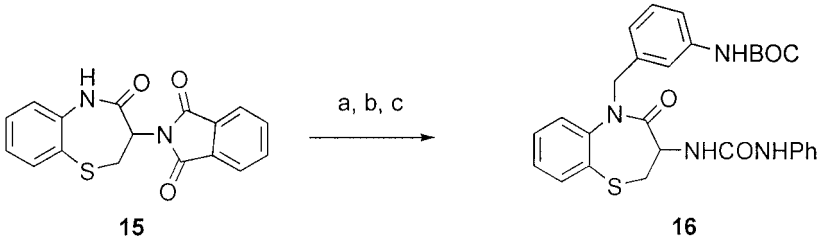
Scatchard plot analysis of the saturation binding experiment is shown in Figure 2. The presence of the compound **10s** or **14c** reduced the K_d value without alteration of maximum binding, suggesting competitive antagonism. The compounds (**10s** and **14c**) were subjected to other NPY receptor (Y2 and Y5) binding assays for assessing Y1 selectivity. There was no affinity for either receptor ($IC_{50} > 10000$ nM). Finally, the effect of the compounds on the functional activity of NPY was examined. Either **10s** or **14c** (1 μM) almost completely abolished the NPY (100 nM)-induced increase in cytosolic free Ca^{2+} concentration. In contrast, either compound scarcely affected basal Ca^{2+} levels or the endothelin-1 (10 nM)-induced Ca^{2+} mobilization (data not shown). Thus our compounds may be selective NPY Y1 receptor antagonists.

Conclusion

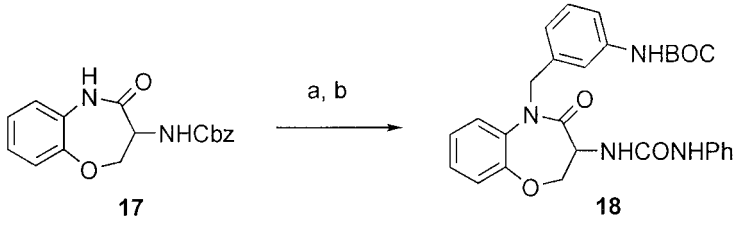
We have discovered novel 1,3-disubstituted-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-ones which are potent and selective NPY Y1 receptor antagonists. SAR studies revealed that introducing the 3-(*N*-(*tert*-butoxycarbonyl)amino)benzyl group at R_1 and 3-((benzothiazol-6-yl)urea) and 3-(*N*-(4-hydroxyphenyl)guanidino) groups at R_3 in structure **1** was advantageous for NPY Y1 receptor binding. However, the NPY Y1 binding affinity of the compounds, **10s** and **14c**, is not satisfactory, and further pharmacological evaluations and further chemical optimization, particularly at the R_1 position, may be needed.



Scheme 4. *Reagents:* (a) MeCOCl, Et_3N or ClCOOMe, Et_3N, THF; (b) $R_3'NHC(SMe)=NH{\cdot}HI$, EtOH, △: or (i) $R_3'NCS$; (ii) 1. MeI, 2. K_2CO_3; (iii) amines, △.



Scheme 5. *Reagents:* (a) N_2H_4, EtOH; (b) PhNCO; (c) Method A.



Scheme 6. *Reagents:* (a) (i) Method A; (ii) H_2, 5% Pd-C, MeOH; (b) PhNCO.

Experimental

General methods

Melting points are not corrected. ^{1}H NMR spectra were recorded on a Varian VXR-200 and VXR-300 FT–^{1}H NMR spectrometer with tetramethylsilane (TMS) as an internal reference. Fast atom bombardment mass spectra (FABMS) and high-resolution (HR)–FABMS were determined using *m*-nitrobenzyl alcohol as a matrix. Silica gel used for column chromatography was Kiesegel 60 (Merck). Preparative thin layer chromatography (PLC) was carried out on E. Merck 60F-254 precoated plate (0.5 mm thickness). Unless otherwise stated, all reactions were carried out under nitrogen atmosphere with anhydrous solvents that had been dried over 4 Å molecular sieves. After extraction of the reaction mixture, the solution was washed with water, dried over Na_2SO_4 or $MgSO_4$ and concentrated at reduced pressure. These procedures are simply indicated by the phrase 'the extracts were treated as usual' unless otherwise noted.

The following compounds were prepared by literature methods: 2-(*tert*-butyldimethylsilyloxy)aniline,[22] 4-(2*H*-tetrazol-5-yl)aniline,[23] 5-amino-benzotriazol,[24] 6-benzothiazolamine,[25] 2-bromo-1-*o*-tolyl-ethanone.[26]

3-(*N*-(*tert*-Butoxycarbonyl)amino)benzyl alcohol (3). This compound was prepared from 3-amino benzylalcohol (2.5 g, 20.3 mmol) and $(BOC)_2O$ (7.2 g, 33.0 mmol) in the usual manner. 96% yield: mp 85–86°C; ^{1}H NMR ($CDCl_3$) δ: 1.52 (9H, s), 1.76 (1H, s), 4.66 (2H, s), 6.52 (1H, brs), 7.04 (1H, m), 7.18–7.32 (2H, m), 7.44 (1H, brs). Anal. ($C_{12}H_{17}NO_3{\cdot}0.1H_2O$); calcd: C, 64.04; H, 7.70; N, 6.22. Found: C, 63.89; H, 7.65; N, 6.23.

3-(*N*-(*tert*-Butoxycarbonyl)amino)benzyl bromide (4). To compound **3** (4.35 g, 19.5 mmol) in CH_2Cl_2 (20 mL) were added PPh_3 (5.82 g, 22.2 mmol) and NBS (3.95 g, 22.2 mmol). The mixture was stirred for 2 h and *n*-hexane (250 mL) was added. The resulting precipitate was filtered off, and the filtrate was concentrated. The residue was purified by column chromatography (EtOAc:*n*-hexane = 1:10) and crystallized from CH_2Cl_2–*n*-hexane to afford **4** (3.95 g, 71%) as crystals: mp 124–125°C; ^{1}H NMR ($CDCl_3$) δ:1.52 (9H, s), 4.46 (2H, s), 6.51 (1H, brs), 7.06 (1H, m), 7.16–7.31 (2H, m), 7.51 (1H, t, J = 1.8 Hz). Anal. ($C_{12}H_{16}NO_2Br$); calcd: C, 50.37; H, 5.64; N, 4.89; Br, 27.92. Found: C, 50.47; H, 5.70; N, 4.94; Br, 27.83.

Method A. 3-Azide-1-*N*-(3-(*N*′-(*tert*-butoxycarbonyl)-amino)benzyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one. A suspension of compound **4** (3.26 g, 11.4 mmol), **7b**

Table 1. In vitro NPY Y1 receptor binding affinity (**11a–n**)

Compounds	R_1	IC_{50} (μM)[a]
11a	CH_2COO*tert*-Bu	> 10
11b	CH_2CONHtert-Bu	> 10
11c	(1-Naphthyl)methyl	> 10
11d	(4-*tert*-Bu)benzyl	> 10
11e	(2-Quinolinyl)methyl	> 10
11f	benzhydlyl	> 10
11g	(4,4′-F_2)benzhydlyl	> 10
11h	(4-Ph)benzyl	> 10
11i	(2-Ph)benzyl	> 10
11j	(4-Bn)benzyl	> 10
11k	(4-OH)benzyl	> 10
11l	(2-Tolyl)carbonylmethyl	> 10
11m	(3-NO_2)benzoylmethyl	> 10
11n	*N*-Phthaloymethyl	> 10

[a] Binding results are the means of two independent determinations.

Table 2. In vitro NPY Y1 receptor binding affinity (**9**, **10a–s**)

Compounds	R	R_3	IC_{50} (μM)[a]
9	OMe	NHCONHMe	1.6
10a	H	NHCONHMe	1.3
10b	H	NHCONH*i*Pr	4.9
10c	H	NHCONH*tert*-Bu	> 10
10d	H	NHCONH-cyclohexyl	> 10
10e	H	NHCONHPh	0.87
10f	H	$NHCONHCH_2Ph$	1.3
10g	H	$NHCONMe_2$	> 10
10h	H	$NHCONHC_6H_4$(2-OH)	6.4
10i	H	$NHCONHC_6H_4$(3-OH)	2.3
10j	H	$NHCONHC_6H_4$(4-OH)	0.36
10k	H	$NHCONHC_6H_4$(4-COOH)	> 10
10l	H	$NHCONHC_6H_4$(4-tetrazolyl)	2.6
10m	H	$NHCONHC_6H_4$(4-OSO_3Na)	4.5
10n	H	NHCONH(3-pyridinyl)	2.4
10o	H	NHCONH(2-pyrimidinyl)	> 10
10p	H	NHCONH(5-(3-*tert*-Bu-isoxazolyl))	2.4
10q	H	NHCONH(5-benzimidazolyl)	1.0
10r	H	NHCONH(6-benzotriazolyl)	0.7
10s	H	NHCONH(6-benzothiazolyl)	0.18

[a] Binding results are the means of two independent determinations.

Table 3. In vitro NPY Y1 receptor binding affinity (**12**, **13**, and **14a–g**)

Compounds	R_3	IC_{50} (μM)[a]
12	NHCOMe	2.9
13	NHCOOMe	5.6
14a	NHC(-NH_2) = NMe	0.34
14b	NHC(-NH_2) = NPh	0.32
14c	NHC(-NH_2) = NC_6H_4(4-OH)	0.043
14d	NHC(-NHMe) = NPh	0.081
14e	NHC(-NHOMe) = NPh	> 10
14f	NHC(-NHOH) = NPh	1.4
14g	NHC(-NMe_2) = NPh	> 10

[a] Binding results are the means of two independent determinations.

Table 4. In vitro NPY Y1 receptor binding affinity (**16** and **18**)

Compound	IC_{50} (μM)[a]
16	1.5
18	> 10

[a] Binding results are the means of two independent determinations.

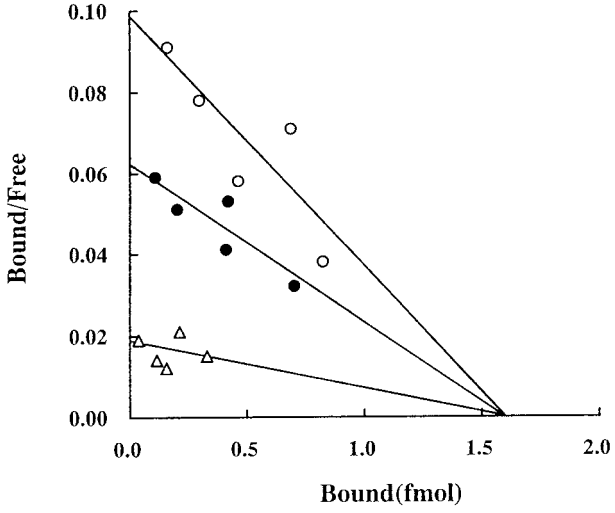


Figure 2. Scatchard plot analysis. [^{125}I]PYY binding to SK-N-MC cells was performed in the absence (○) or presence of **10s** (200 nM, ●) or **14c** (50 nM, △).

(2.0 g, 9.89 mmol) and tetrabutylammonium bromide (0.33 g, 0.99 mmol) in THF (125 mL) was added to powdered KOH (742 mg, 11.4 mmol) at 0°C and stirred at rt for 2 h. The reaction mixture was neutralized by 0.5 N HCl and extracted with EtOAc. The extracts were treated as usual. The residue was purified by column chromatography (Et_2O:*n*-hexane = 1:2) to afford 3.80 g (96%) of the target compound as a powder: ^{1}H NMR ($CDCl_3$) δ: 1.50 (9H, s), 2.24–2.70 (4H, m), 3.76 (1H, t, J = 9.0 Hz), 4.85 (1H, d, J = 14.7 Hz), 5.17 (1H, d, J = 14.7 Hz), 6.43 (1H, s), 6.86 (1H, d, J = 7.5 Hz), 7.16–7.41 (7H, m).

3-Amino-1-*N*-(3-(*N*′-(*tert*-butoxycarbonyl)amino)benzyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (8b). The above 3-azide compound (3.79 g, 9.49 mmol) was hydrogenated in MeOH (35 mL) with 10% Pd-C (370 mg) under hydrogen atmosphere at rt overnight. After removal of the catalyst by filtration, the filtrate was evaporated to dryness to give **8b** (4.09 g, quant.) as a powder: ^{1}H NMR ($CDCl_3$) δ: 1.46 (9H, s), 2.21–2.66 (4H, m), 3.83 (1H, m), 4.72 (1H, d, J = 15.3 Hz), 5.00 (1H, d, J = 15.6 Hz), 6.76 (1H, d, J = 7.2 Hz), 7.00–7.19 (5H, m), 7.43–7.55 (2H, m). Anal. ($C_{22}H_{27}N_3O_3 \cdot 0.9H_2O$); calcd: C, 66.44; H, 7.30; N, 10.57. Found: C, 66.35; H, 7.02; N, 10.58.

Compound **8a** was prepared from **7a** according to a similar procedure.

3-Amino-1-*N*-(3-(*N*′-(*tert*-butoxycarbonyl)amino)benzyl)-7-methoxy-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (8a). ^{1}H NMR ($CDCl_3$) δ: 1.50 (9H, s), 2.16–2.69 (4H, m), 3.75 (1H, dd, J = 7.6 Hz, 15.3 Hz), 3.79 (3H, s), 4.76 (1H, d, J = 14.4 Hz), 5.15 (1H, d, J = 14.4 Hz), 6.44 (1H, brs), 6.67 (1H, d, J = 2.8 Hz), 6.78 (1H, dd, J = 3.0 Hz,

8.8 Hz), 6.86 (1H, td, J = 1.2 Hz, 7.7 Hz), 7.10 (1H, d, J = 8.8 Hz), 7.13 (1H, m), 7.17 (1H, t, J = 7.8 Hz), 7.40 (1H, m). Anal. ($C_{23}H_{27}N_5O_4$); calcd: C, 63.14; H, 6.22; N, 16.01. Found: C, 63.05; H, 6.33; N, 15.78.

Method B. Preparation of 1-*N*-(3-(*N*′-(*tert*-butoxycarbonyl)amino)benzyl)-3-(3-phenylureido)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (10e). A solution of phenylisocyanate (45 μL, 0.412 mmol) in DMF (0.5 mL) was added to a solution of compound **8b** (150 mg, 0.393 mmol) in DMF (3 mL) at 0°C. The mixture was stirred at rt overnight and diluted with water and extracted with EtOAc. The extracts were treated as usual. The residue was purified by column chromatography (Et_2O: *n*-hexane = 3:2) to afford **10e** (137 g, 70%) as a powder: mp 139°C (dec.); ^{1}H NMR ($CDCl_3$) δ: 1.50 (9H, s), 1.99 (1H, m), 2.59 (2H, m), 2.80 (1H, m), 4.65 (1H, m), 4.79 (1H, d, J = 15.6 Hz), 5.35 (1H, d, J = 15.6 Hz), 6.54 (1H, brs), 6.80–7.03 (8H, m), 7.35 (1H, brs), 7.62 (1H, brd, J = 7.8 Hz). Anal. ($C_{29}H_{32}N_4O_4{\cdot}0.1H_2O$); calcd: C, 69.69; H, 6.71; N, 10.87. Found: C, 69.77; H, 6.89; N, 10.83.

Compounds **9** (from **8a**) and **10a**–**d**,**f** (from **8b**) were prepared according to a similar procedure.

1-*N*-(3-(*N*′-(*tert*-Butoxycarbonyl)amino)benzyl)-7-methoxy-3-(3-methylureido)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (9). 79% yield: mp 209–210°C; ^{1}H NMR ($CDCl_3$) δ: 1.48 (9H, s), 1.94 (1H, dt, J = 7.4 Hz, 11.1 Hz), 2.36–2.82 (3H, m), 2.61 (3H, s), 3.79 (3H, s), 4.55 (1H, m), 4.72 (1H, brs), 4.76 (1H, d, J = 15.2 Hz), 5.18 (1H, d, J = 15.2 Hz), 5.95 (1H, brs), 6.71 (1H, s), 6.73 (1H, dd, J = 2.8 Hz, 8.6 Hz), 6.86 (1H, brd, J = 7.8 Hz), 7.00 (1H, dd, J = 1.8 Hz, 7.2 Hz), 7.13 (1H, m), 7.17 (1H, brs), 7.23 (1H, t, J = 7.8 Hz), 7.59 (1H, brd, J = 7.8 Hz). Anal. ($C_{25}H_{32}N_4O_5{\cdot}0.2H_2O$); calcd: C, 63.60; H, 6.92; N, 11.87. Found: C, 63.62; H, 6.97; N, 12.07.

1-*N*-(3-(*N*′-(*tert*-Butoxycarbonyl)amino)benzyl)-3-(3-methylureido)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (10a). 69% yield: ^{1}H NMR ($CDCl_3$) δ: 1.47 (9H, s), 2.00 (1H, m), 2.30–2.90 (3H, m), 2.53 (3H, s), 4.62 (1H, m), 4.68 (1H, d, J = 16.2 Hz), 5.38 (1H, d, J = 16.0 Hz), 6.19 (1H, m), 6.86 (1H, d, J = 7.8 Hz), 7.06 (1H, d, J = 8.0 Hz), 7.10–7.30 (5H, m), 7.47 (1H, brs), 7.68 (1H, d, J = 7.8 Hz). Anal. ($C_{24}H_{30}N_4O_4{\cdot}0.2C_6H_6$); calcd: C, 66.65; H, 6.92; N, 12.34. Found: C, 66.31; H, 6.97; N, 12.15.

1-*N*-(3-(*N*′-(*tert*-Butoxycarbonyl)amino)benzyl)-3-(3-isopropylureido)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (10b). 89% yield: mp 209–211°C; ^{1}H NMR ($CDCl_3$) δ: 0.95 (3H, d, J = 6.3 Hz), 1.01 (3H, d, J = 6.3 Hz), 1.48 (9H, s), 1.95 (1H, m), 2.50 (1H, m), 2.76 (2H, m), 3.79 (1H, dq, J = 6.3, 14.4 Hz), 4.57 (1H, m), 4.70 (1H, brs), 4.73 (1H, d, J = 15.9 Hz), 5.31 (1H, d, J = 15.9 Hz), 5.64 (1H, d, J = 8.1 Hz), 6.86 (1H, d, J = 7.5 Hz), 7.06 (1H, d, J = 8.1 Hz), 7.20 (7H, m), 7.62 (1H, d, J = 8.1 Hz). Anal. ($C_{26}H_{34}N_4O_4$); calcd: C, 66.93; H, 7.34; N, 12.01. Found: C, 66.91; H, 7.40; N, 12.01.

1-*N*-(3-(*N*′-(*tert*-Butoxycarbonyl)amino)benzyl)-3-(3-*tert*-butylureido)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (10c). 84% yield: mp 202–205°C; ^{1}H NMR ($CDCl_3$) δ: 1.24 (9H, s), 1.49 (9H, s), 1.93 (1H, m), 2.50 (2H, m), 2.70 (1H, m), 4.52 (1H, m), 4.65 (1H, s), 4.74 (1H, d, J = 15.9 Hz), 5.29 (1H, d, J = 15.9 Hz), 5.35 (1H, d, J = 8.1 Hz), 6.85 (1H, d, J = 7.5 Hz), 6.96 (1H, s), 7.06 (1H, d, J = 7.5 Hz), 7.20 (9H, m), 7.59 (1H, d, J = 7.5 Hz). Anal. ($C_{27}H_{36}N_4O_4$); calcd: C, 67.48; H, 7.55; N, 11.66. Found: C, 67.35; H, 7.73; N, 11.49.

1-*N*-(3-(*N*′-(*tert*-Butoxycarbonyl)amino)benzyl)-3-(3-cyclohexylureido)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (10d). 78% yield: mp 198–201°C; ^{1}H NMR ($CDCl_3$) δ: 0.85–1.35 (4H, m), 1.49 (9H, s), 1.50–2.00 (7H, m), 2.40–2.80 (3H, m), 3.40 (1H, m), 4.55 (1H, dd, J = 7.5, 11.1 Hz), 4.79 (1H, d, J = 15.3 Hz), 5.25 (1H, d, J = 15.3 Hz), 5.60 (1H, brs), 6.86 (1H, d, J = 8.1 Hz), 7.00 (1H, s), 7.09–7.40 (7H, m), 7.57 (1H, d, J = 7.5 Hz). Anal. ($C_{29}H_{38}N_4O_4$); calcd: C, 68.75; H, 7.56; N, 11.06. Found: C, 68.54; H, 7.65; N, 11.01.

3-(3-Benzylureido)-1-*N*-(3-(*N*′-(*tert*-butoxycarbonyl)amino)benzyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (10f). 99% yield: ^{1}H NMR ($CDCl_3$) δ: 1.41 (9H, s), 1.71 (1H, m), 1.92 (1H, m), 2.48 (2H, m), 2.68 (1H, m), 4.08 (1H, m), 4.38 (1H, dd, J = 6.4, 15.0 Hz), 4.67 (1H, d, J = 16.2 Hz), 5.20 (1H, d, J = 15.6 Hz), 5.42 (1H, brs), 6.10 (1H, brs), 6.80 (1H, d, J = 7.8 Hz), 7.05 (1H, d, J = 7.5 Hz), 7.12–7.21 (10H, m), 7.58 (1H, brd, J = 7.8 Hz). Anal. ($C_{30}H_{34}N_4O_4$); calcd: C, 70.02; H, 6.66; N, 10.89. Found: C, 69.93; H, 6.88; N, 10.77.

Method C1. Preparation of 1-*N*-(3-(*N*′-(*tert*-butoxycarbonyl)amino)benzyl)-3-(3-phenylureido)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (10g). To a solution of compound **8b** (200 mg, 0.524 mmol) in CH_3CN (6 mL) was added carbonyldiimidazole (170 mg, 1.05 mmol) at 0°C and the mixture was stirred at rt for 1 h. The reaction mixture was poured into water and extracted with EtOAc. The extracts were treated as usual. Dimethylamine (1 M) in THF solution (0.25 mL) was added to the residue. The reaction mixture was stirred at rt for 18 h, acidified with 10% HCl and extracted with EtOAc. The extracts were treated as usual to give **10g** (46%): ^{1}H NMR ($CDCl_3$) δ: 1.49 (9H, s), 2.00 (1H, m), 2.48–2.58 (2H, m), 2.73 (1H, m), 4.53 (1H, m), 4.83 (1H, d, J = 15.3 Hz), 5.19 (1H, d, J = 15.6 Hz), 6.85 (1H, d, J = 7.8 Hz), 6.99 (1H, s), 7.07–7.27 (7H, m), 7.37 (1H, brd, J = 7.5 Hz). Anal. ($C_{25}H_{32}N_4O_4{\cdot}0.3H_2O$); calcd: C, 65.57; H, 7.18; N, 12.23. Found C, 65.57; H, 7.17; N, 12.25.

1-*N*-(3-(*N*′-(*tert*-Butoxycarbonyl)amino)benzyl)-3-(pyrimidin-2-yl)phenylureido)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (10o). This compound was prepared according to Method C1 from **8b** and 2-aminopyrimidine instead of dimethylamine. 35% yield: mp 168–170°C; ^{1}H NMR ($CDCl_3$) δ: 1.49 (9H, s), 2.11 (1H, m), 2.56 (2H, m), 2.70 (1H, m), 4.50 (1H, dd, J = 7.2 Hz, 9.0 Hz), 4.82 (1H, d, J = 15.0 Hz), 5.31 (1H, d, J = 15.0 Hz), 6.86 (1H, d, J = 9.0 Hz), 7.04 (1H, t, J = 5.1 Hz), 7.13 (1H, t, J = 9.0 Hz), 7.10–7.40 (6H, m), 8.56 (2H, d, J = 5.1 Hz). Anal. ($C_{27}H_{30}N_6O_4{\cdot}0.2H_2O$); calcd: C, 64.07; H, 6.05; N, 16.60. Found: C, 63.99; H, 6.10; N, 16.72.

Method C2. Preparation of 1-*N*-(3-(*N*′-(*tert*-butoxycarbonyl)amino)benzyl)-3-(3-(4-hydroyxy)phenylureido)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (10j)

3-(3-(4-Benzyloxy)phenylureido)-1-*N*-(3-(*N*′-(*tert*-butoxycarbonyl)amino)benzyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one. A mixture of 4-benzyloxyaniline hydrochlroride (300 mg, 1.27 mmol) and carbonyldiimidazole (207 mg, 1.27 mmol) in THF (10 mL) was stirred at rt and Et_3N (0.18 mL, 1.3 mmol) was added dropwise. The mixture was stirred for 1.5 h and filtered. The filtrate was washed with $CHCl_3$ and evaporated. Compound **8b** (100 mg, 0.262 mmol) in DMF (3 mL) and Et_3N (0.4 mL, 2.87 mmol) was added dropwise to the residue. The mixture was stirrred for 16 h. Water was added and the mixture was filtered. The residue was dried and purified by column chromatography (EtOAc:*n*-hexane = 1:2) to afford 128 mg (80%) as a powder: ^{1}H NMR ($CDCl_3$) δ: 1.49 (9H, s), 1.96 (1H, m), 2.49–2.63 (2H, m), 2.75 (1H, m), 4.62 (1H, m), 4.80 (1H, d, J = 15.9 Hz), 4.94 (2H, s), 5.29 (1H, d, J = 14.7 Hz), 6.38 (1H, brs), 6,68 (2H, dd, J = 1.8 Hz, 8.7 Hz), 6.88 (3H, m), 7.12–7.39 (13H, m), 7.57 (1H, brd, J = 8.7 Hz). Anal. ($C_{36}H_{38}N_4O_5$); calcd: C, 71.27; H, 6.31; N, 9.23. Found: C, 71.10; H, 6.58; N, 9.03.

1-*N*-(3-(*N*′-(*tert*-Butoxycarbonyl)amino)benzyl)-3-(3-(4-hydroxy)phenylureido)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (10j). The above *O*-benzyl compound (128 mg, 0.211 mmol) was hydrogenated in MeOH (4.5 mL) with 10% Pd-C (18 mg) under hydrogen atmosphere at rt for 4 h. After removal of the catalyst by filtration, the filtrate was evaporated to dryness. The residue was purified by column chromatography ($CHCl_3$:MeOH = 48:1) to afford **10j** (103 mg, 95%) as a powder: ^{1}H NMR ($CDCl_3$) δ: 1.45 (9H, s), 1.98 (1H, m), 2.54 (3H, m), 4.54 (1H, m), 4.87 (1H, d, J = 15.6 Hz), 5.02 (1H, d, J = 15.6 Hz), 6.38 (1H, d, J = 7.8 Hz), 6.46 (1H, d, J = 15.6 Hz), 6.80 (3H, m), 6.91 (1H, m), 7.34 (1H, d, J = 8.6 Hz), 7.47–7.54 (1H, m), 7.04–7.54 (7H, m). Anal. ($C_{29}H_{32}N_4O_5 \cdot 0.15C_6H_{14} \cdot 0.1H_2O$); calcd: C, 67.59; H, 6.51; N, 10.54. Found: C, 67.66; H, 6.75; N, 10.51.

1-*N*-(3-(*N*′-(*tert*-Butoxycarbonyl)amino)benzyl)-3-(3-(3-hydroxy)phenylureido)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (10i). 1-*N*-(3-(*N*′-(*tert*-Butoxycarbonyl)-amino)benzyl)-3-(3-(3-tetrahydopyranoxy)phenylureido)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one was prepared according to method C2 from compound **8b** (100 mg, 0.26 mmol) and (3-tetrahydopyranoxy)phenol (65.6 mg, 0.34 mmol), obtained from 3-amino phenol, and then removal of the THP group in the usual manner with *p*-TsOH·H_2O to give **10i** (35%): ^{1}H NMR ($CDCl_3$) δ: 1.59 (9H, s), 2.02 (1H, m), 2.50–2.91 (3H, m), 4.59 (3H, m), 6.30 (1H, d, J = 9.4 Hz), 6.71 (3H, m), 6.93 (1H, brd, J = 7.8 Hz), 7.05 (1H, brs), 7.17–7.39 (6H, m), 7.51 (1H, d, J = 8.2 Hz). Anal. ($C_{29}H_{32}N_4O_5 \cdot 0.3H_2O$); calcd: C, 66.73; H, 6.29; N, 10.73. Found: C, 66.69; H, 6.44; N, 10.81.

Method D. Preparation of 3-(3-(benzothiazol-6-yl)-ureido)-1-*N*-(3-(*N*′-(*tert*-butoxycarbonyl)amino)benzyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (10s). A suspension of triphosgene (28 mg, 0.094 mmol) and 6-benzothiazolamine (100 mg, 0.262 mmol) in CH_2Cl_2 (3 mL) was cooled to −20°C, and Et_3N (40 μL, 0.287 mmol) was added dropwise. The mixture was stirred for 30 min. Compound **8b** (45 mg, 0.118 mmol) was added. Et_3N (77 μL, 0.552 mmol) was added dropwise, followed by stirring at −20°C for 2.5 h. Ice-water was added. Extractive work up with EtOAc and PLC ($CHCl_3$:acetone = 10:1) afforded **10s** (73 mg, 50%) as a powder: ^{1}H NMR ($CDCl_3$) δ: 1.51 (9H, s), 2.03 (1H, m), 2.60 (1H, m), 2.70 (1H, m), 2.86 (1H, m), 4.76 (1H, d, J = 15.9 Hz), 5.48 (1H, d, J = 15.9 Hz), 6.81 (1H, d, J = 11.1 Hz), 6.89 (1H, d, J = 8.4 Hz), 6.99 (1H, d, J = 8.4 Hz), 7.02 (1H, s), 7.19–7.35 (6H, m), 7.53 (1H, d, J = 9.0 Hz), 7.58 (1H, d, J = 7.8 Hz), 7.71 (1H, s), 8.61 (1H, s). Anal. ($C_{30}H_{31}N_5O_4S \cdot 0.4H_2O$); calcd: C, 63.79; H, 5.67; N, 12.40; S, 5.68. Found: C, 63.82; H, 5.85; N, 12.36; S, 5.74.

Compounds **10l, 10n, 10p,** and **10r** were prepared from **8b** according to a similar procedure.

1-*N*-(3-(*N*′-(*tert*-Butoxycarbonyl)amino)benzyl)-3-(3-(4-1*H*-tetrazol-5-yl)phenylureido)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (10l). 43% yield: ^{1}H NMR ($CDCl_3$ + CD_3OD) δ: 1.37 (9H, s), 2.05 (1H, m), 2.68–2.78 (2H, m), 2.90 (1H, m), 4.59 (1H, m), 4.69 (1H, d, J = 16.2 Hz), 5.57 (2H, m), 6.76 (2H, brs), 7.01 (1H, brd, J = 7.2 Hz), 7.18–7.33 (9H, m), 7.59 (1H, s), 8.06 (1H, brs). Anal. ($C_{30}H_{32}N_8O_4 \cdot 0.2C_6H_{14} \cdot 0.6H_2O$); calcd: C, 62.80; H, 6.08; N, 18.78. Found: C, 62.57; H, 6.04; N, 18.69.

1-*N*-(3-(*N*′-(*tert*-Butoxycarbonyl)amino)benzyl)-3-(3-(pyridin-3-yl)phenylureido)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (10n). 26% yield: ^{1}H NMR ($CDCl_3$) δ: 1.50 (9H, s), 1.97 (1H, m), 2.53–2.62 (2H, m), 2.74 (1H, m), 4.60 (1H, m), 4.90 (1H, d, J = 15.6 Hz), 5.23 (1H, d, J = 15.3 Hz), 6.54 (1H, d, J = 7.5 Hz), 6.87 (1H, d, J = 7.5 Hz), 6.97 (1H, m), 7.11 (1H, brs), 7.23 (5H, m), 7.50 (2H, d, J = 8.4 Hz), 7.64 (1H, brs), 8.10 (1H, d, J = 3.9 Hz), 8.29 (1H, brs). Anal. ($C_{28}H_{31}N_5O_4 \cdot 0.5H_2O$); calcd: C, 65.87; H, 6.32; N, 13.72. Found: C, 66.16; H, 6.49; N, 13.53.

3-(3-((5-*tert*-Butyl)isoxazol-3-yl)phenylureido)-1-*N*-(3-(*N*′-(*tert*-butoxycarbonyl)amino)benzyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (10p). 60% yield: ^{1}H NMR ($CDCl_3$) δ: 1.29 (9H, s), 1.48 (9H, s), 2.02 (1H, m), 2.46–2.64 (3H, m), 4.54 (1H, m), 4.92 (1H, d, J = 14.7 Hz), 5.19 (1H, d, J = 14.7 Hz), 6.10 (1H, s), 6.72 (1H, s), 6.83 (1H, d, J = 7.8 Hz), 7.14–7.26 (6H, m), 7.48 (1H, d, J = 7.2 Hz), 7.54 (1H, brs), 8.17 (1H, brs). Anal. ($C_{30}H_{37}N_5O_5 \cdot 0.1H_2O$); calcd: C, 65.58; H, 6.82; N, 12.75. Found: C, 65.58; H, 6.85; N, 12.86.

3-(3-(Bezotriazol-5-yl)phenylureido)-1-*N*-(3-(*N*′(*tert*-butoxycarbonyl)amino)benzyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (10r). 41% yield: ^{1}H NMR ($CDCl_3$) δ: 1.20 (9H, d, J = 7.5 Hz), 2.11 (1H, m), 2.52–2.66 (2H, m), 2.81 (1H, m), 4.66 (1H, m), 4.85 (1H, brs), 5.35 (1H, brs), 6.63 (1H, brs), 6.94 (2H, d, J = 15.9 Hz), 7.01 (1H, brs), 7.22 (2H, m), 7.42 (2H, s), 7.51 (1H, br, s), 8.65

(2H, s). Anal. ($C_{29}H_{31}N_7O_4 \cdot 0.1C_6H_{14} \cdot 0.4H_2O$); calcd: C, 63.79; H, 6.00; N, 17.58. Found: C, 63.87; H, 6.21; N, 17.67.

1-*N*-(3-(*N*′(*tert*-Butoxycarbonyl)amino)benzyl)-3-(3-(2-hydroxy)phenylureido)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (10h). 1-*N*-(3-(*N*′-(*tert*-Butoxycarbonyl)-amino)benzyl)-3-(3-(2-*tert*-butyldimethylsilyloxy)phenylureido)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one was prepared according to Method D from compound **8b** (100 mg, 0.262 mmol) and (2-*tert*-butyldimethylsilyloxy)-phenol (39 mg, 0.174 mmol) and then removal of the TBDMS group in the usual manner with *n*-BuN^+F^- gave **10h** (58%): ^{1}H NMR ($CDCl_3$) δ: 1.51 (9H, s), 2.00 (1H, m), 2.51–2.77 (3H, m), 4.56 (1H, m), 5.31 (2H, d, J = 15.4 Hz), 6.62 (1H, m), 6.85 (4H, m), 7.08–7.23 (6H, m), 7.54–7.63 (2H, m). Anal. ($C_{29}H_{32}N_4O_5 \cdot 0.1C_6H_{14} \cdot 0.3H_2O$); calcd: C, 67.00; H, 6.46; N, 10.5. Found: C, 67.11; H, 6.75; N, 10.75.

3-(3-(Benzimidazol-5-yl)phenylureido)-1-*N*-(3-(*N*′-(*tert*-butoxycarbonyl)amino)benzyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (10q). 1-*N*-(3-(*N*′-(*tert*-Butoxycarbonyl)amino)benzyl)-3-(3-(*p*-tosyl[1*H*]-benzimidazol-5-yl)phenylureido)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one was prepared according to Method D from compound **8b** (250 mg, 0.655 mmol) and 5-amino-1-(*p*-tosyl)bezimidazole (180 mg, 0.72 mmol) and then the tosyl group was removed in the usual manner with 10% KOH/MeOH to give **10q** (26%): ^{1}H NMR ($CDCl_3$) δ: 1.48 (9H, s), 2.01 (1H, m), 2.49–2.61 (2H, m), 2.77 (1H, m), 4.60 (1H, m), 4.77 (1H, m), 5.28 (1H, brs), 6.69 (1H, brs), 6.88 (2H, brd, J = 8.4 Hz), 7.10–7.26 (8H, m), 7.34 (1H, s), 7.47 (1H, m), 7.67–7.81 (1H, m). Anal. ($C_{30}H_{32}N_6O_4 \cdot 1.2H_2O$); calcd: C, 64.09; H, 6.17; N, 14.95. Found: C, 64.03; H, 6.00; N, 15.02.

Method E. 1-*N*-(3-(*N*′-(*tert*-Butoxycarbonyl)amino)-benzyl)-3-(3-(4-carboxyphenylureido)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (10k). To a solution of compound **8b** (70 mg, 0.183 mmol) and 4-phenoxycarbonylaminobenzoic acid (50 mg, 0.195 mmol) in DMF (3 mL) was added Et_3N and the mixture was stirred at rt for 18 h. 10% HCl was added to the mixture and the resulting precipitation was filtered. The residue was purified by column chromatography ($CHCl_3$:MeOH = 20:1) to afford **10k** (46%): ^{1}H NMR ($CDCl_3$) δ: 1.45 (18H, s), 1.91 (2H, m), 2.31–2.61 (6H, m), 4.37 (2H, m), 4.84 (2H, d, J = 14.8 Hz), 5.16 (2H, d, J = 15.2 Hz), 6.15 (2H, brs), 6.75 (2H, d, J = 7.6 Hz), 6.97–7.16 (14H, m), 7.52 (2H, brd, J = 7.8 Hz). Anal. ($C_{45}H_{52}N_6O_7 \cdot 0.1C_6H_{14} \cdot 0.8H_2O$); calcd: C, 67.45; H, 6.83; N, 10.35. Found: C, 67.34; H, 6.85; N, 10.12.

1-*N*-(3-(*N*′-(*tert*-Butoxycarbonyl)amino)benzyl)-3-(3-(4-sulfonyloxy)phenylureido)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one sodium salt (10m). To a solution of compound **10j** (100 mg, 0.193 mmol) in pyridine (4 mL) was added sulfur trioxide pyridine complex (154 mg, 0.97 mmol). The mixture was stirred for 110 h and then concentrated and water was added. The mixture was filtered and then concentrated. The residue was dissolved in 1 N NaOH (3.5 mL) and the solution was washed with $CHCl_3$. The aqueous phase was extracted with 1-butanol twice, and the extracts were treated as usual to afford 290 mg (50%) of the target compound: ^{1}H NMR ($CDCl_3$) δ: 1.49 (9H, s), 2.00 (1H, m), 2.36–2.69 (3H, m), 4.35 (1H, m), 4.82 (1H, d, J = 15.4 Hz), 5.27 (1H, d, J = 14.8 Hz), 6.84 (1H, brd, J = 7.4 Hz), 7.08–7.35 (11H, m). Anal. ($C_{29}H_{31}N_4O_8Na \cdot 2.2H_2O$); calcd: C, 52.91; H, 5.42; N, 8.51; S, 4.87. Found: C, 52.79; H, 5.35; N, 8.49; S, 5.26.

Compounds **11a–i**, **11l–n** were prepared according to Method A from **7b**.

1-*N*-(3-(*N*′-(*tert*-Butoxycarbonyl)amino)benzyl)-3-(3-methylureido)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (11a). 98% yield: mp 229–230°C; ^{1}H NMR ($CDCl_3$) δ: 1.43 (9H, s), 2.00 (1H, m), 2.60 (2H, m), 2.74 (3H, d, J = 4.8 Hz), 3.35 (1H, m), 4.21 (1H, d, J = 16.8 Hz), 4.45 (1H, m), 4.48 (1H, m), 4.69 (1H, d, J = 17.1 Hz), 5.59 (1H, d, J = 6.6 Hz), 7.12 (1H, d, J = 8.4 Hz), 7.19–7.29 (3H, m). Anal. ($C_{18}H_{25}N_3O_4 \cdot 1.0H_2O$); calcd: C, 59.16; H, 7.44; N, 11.51. Found: C, 58.86; H, 7.18; N, 11.52.

1-*N*-(3-(*N*′-(*tert*-Butoxycarbamoylmethyl)amino)benzyl)-3-(3-methylureido)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (11b). 94% yield: ^{1}H NMR ($CDCl_3$) δ: 1.19 (9H, s), 2.14–2.31 (1H, m), 1.78–1.89 (1H, m), 2.50–2.58 (4H, m), 3.17–3.28 (1H, m), 4.05–4.15 (1H, m), 4.19 (1H, d, J = 15.9 Hz), 4.43 (1H, d, J = 16.2 Hz), 5.95–6.00 (1H, m), 6.14 (1H, d, J = 8.1 Hz), 7.17–7.35 (3H, m). Anal. ($C_{18}H_{26}N_4O_3 \cdot 0.15CHCl_3$); calcd: C, 59.83; H, 7.23; N, 15.38. Found: C, 59.77; H, 7.25; N, 15.52.

3-(3-Methylureido)-1-*N*-((1-naphthyl)methyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (11c). 83% yield: ^{1}H NMR ($CDCl_3$) δ: 1.87 (1H, m), 2.34 (1H, m), 2.51 (2H, m), 2.71 (3H, d, J = 5.1 Hz), 4.39 (1H, m), 4.54 (1H, m), 5.35 (1H, d, J = 15.3 Hz), 5.49 (1H, d, J = 8.1 Hz), 5.73 (1H, d, J = 15.3 Hz), 7.06–8.09 (11H, m). Anal. ($C_{23}H_{23}N_3O_2 \cdot 0.15H_2O$); calcd: C, 73.44; H, 6.24; N, 11.17. Found: C, 73.41; H, 6.34; N, 11.17.

1-*N*-(4-(*tert*-Butyl)benzyl)-3-(3-methylureido)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (11d). 93% yield: mp 247–249°C; ^{1}H NMR ($CDCl_3$) δ: 1.28 (9H, s), 1.98 (1H, m), 2.44–2.60 (3H, m), 2.68 (3H, d, J = 4.5 Hz), 4.48 (1H, brs), 4.91 (1H, d, J = 14.7 Hz), 5.09 (1H, d, J = 15.0 Hz), 5.55 (1H, brs), 7.12–7.30 (8H, m). Anal. ($C_{23}H_{29}N_3O_2$); calcd: C, 72.79; H, 7.70; N, 11.07. Found: C, 72.69; H, 7.76; N, 11.04.

3-(3-Methylureido)-1-*N*-((2-quinolinyl)methyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (11e). 83% yield: ^{1}H NMR ($CDCl_3$) δ: 1.93–2.03 (1H, m), 2.57–2.68 (5H, m), 3.14–3.27 (1H, m), 4.47 (1H, brs), 4.53–4.62 (1H, m), 5.27 (1H, d, J = 15.9 Hz), 5.40 (1H, d, J = 15.9 Hz), 5.51 (1H, brs), 7.12–7.23 (4H, m), 7.46 (1H, d, J = 8.4 Hz), 7.51 (1H, t, J = 8.1 Hz), 7.68 (1H, td, J = 1.5, 8.1 Hz), 7.79 (1H, d, J = 7.5 Hz), 7.99 (1H, d, J = 8.4 Hz), 8.13 (1H, d, J = 8.4 Hz). Anal. ($C_{22}H_{23}N_4O_3 \cdot 0.15C_6H_{14} \cdot 0.3H_2O$); calcd: C, 69.85; H, 6.58; N, 14.23. Found: C, 69.64; H, 6.30; N, 13.94.

1-*N*-(Benzhydryl)-3-(3-methylureido)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (11f). 87% yield: ^{1}H NMR ($CDCl_3$) δ: 1.85–1.93 (1H, m), 2.36–2.55 (3H, m), 2.60 (3H, m), 4.52–4.60 (1H, m), 4.56 (1H, brs), 5.70 (1H, brs), 7.00–7.17 (10H, m), 7.31–7.38 (5H, m). Anal. ($C_{25}H_{25}N_3O_2 \cdot 0.15C_6H_{14} \cdot 0.3H_2O$); calcd: C, 74.45; H, 6.68; N, 10.06. Found: C, 74.60; H, 6.87; N, 9.91.

1-*N*-((4,4′-Difluoro)benzhydryl)-3-(3-methylureido)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (11g). 72% yield: mp 235–238°C; ^{1}H NMR ($CDCl_3$) δ: 1.83–1.91 (1H, m), 2.39–2.48 (3H, m), 2.70 (3H, d, J = 5.1 Hz), 4.37 (1H, m), 4.48–4.56 (1H, m), 5.36 (1H, d, J = 8.1 Hz), 6.86 (2H, t, J = 8.7 Hz), 6.95 (1H, d, J = 7.5 Hz), 7.03–7.11 (7H, m), 7.28–7.32 (2H, m). Anal. ($C_{25}H_{23}N_3O_2F_2$); calcd: C, 68.95; H, 5.32; N, 9.65; F, 8.45. Found: C, 69.00; H, 5.58; N, 9.80; F, 8.73.

1-*N*-(*p*-Biphenylmethyl)-3-(3-methylureido)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (11h). 97% yield: ^{1}H NMR ($CDCl_3$) δ: 1.76–1.99 (1H, m), 2.43–2.71 (3H, m), 2.60 (3H, d, J = 5.0 Hz), 4.45–4.58 (1H, m), 4.85 (1H, brs), 4.89 (1H, d, J = 15.6 Hz), 5.16 (1H, d, J = 15.8 Hz), 5.90 (1H, m), 6.81 (1H, d, J = 5.8 Hz), 7.00–7.20 (6H, m), 7.26–7.40 (5H, m), 7.49 (1H, d, J = 7.4 Hz). Anal. ($C_{25}H_{25}N_3O_2 \cdot 0.1C_6H_6 \cdot 0.4H_2O$); calcd: C, 74.04; H, 6.60; N, 10.01. Found: C, 74.06; H, 6.58; N, 10.07.

1-*N*-(*o*-Biphenylmethyl)-3-(3-methylureido)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (11i). 94% yield: ^{1}H NMR ($CDCl_3$) δ: 1.91 (1H, m), 2.41–2.62 (3H, m), 2.72 (3H, d, J = 4.6Hz), 4.38(1H, brs), 4.47–4.54 (1H, m), 4.93 (1H, d, J = 15.2 Hz), 5.22 (1H, d, J = 15.2Hz), 5.44 (1H, d, J = 7.8 Hz), 7.16–7.57 (11H, m). Anal. ($C_{25}H_{25}N_3O_2 \cdot 0.1CHCl_3 \cdot 1.1H_2O$); calcd: C, 69.91; H, 6.38; N, 9.74. Found: C, 69.95; H, 6.10; N, 9.84.

3-(3-Methylureido)-1-*N*-((2-(*o*-methylphenyl-oxo)ethyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (11l). 79% yield: ^{1}H NMR ($CDCl_3 + CD_3OD$) δ: 2.07 (1H, m), 2.41 (3H, m), 2.41–2.70 (3H, m), 2.70 (3H, s), 3.45 (2H, m), 4.50 (1H, brs), 4.86 (1H, d, J = 19.2 Hz), 5.42 (1H, d, J = 19.4 Hz), 6.00 (1H, brs), 7.13–7.45 (6H, m), 7.70 (1H, d, 7.2 Hz). Anal. ($C_{21}H_{23}N_3O_3$); calcd: C, 69.02; H, 6.34; N, 11.50. Found: C, 68.82; H, 6.41; N, 11.60.

3-(3-Methylureido)-1-*N*-((2-(*m*-nitrophenyl-oxo)ethyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (11m). 12% yield: ^{1}H NMR ($CDCl_3 + CD_3OD$) δ: 1.97–2.18 (2H, m), 2.53–2.73 (1H, m), 2.71 (3H, m), 3.42–3.60 (1H, m), 4.48–4.57 (1H, m), 4.54 (1H, d, J = 17.4 Hz), 5.08 (1H, d, J = 17.4 Hz), 7.14–7.28 (4H, m), 7.73 (1H, t, J = 8.0 Hz), 8.31 (1H, d, J = 7.8 Hz), 8.47 (1H, d, J = 7.8 Hz), 8.81 (1H, s). Anal. ($C_{20}H_{20}N_4O_5 \cdot 0.1CHCl_3 \cdot 0.1H_2O$); calcd: C, 58.86; H, 4.99; N, 13.66. Found: C, 58.86; H, 5.10; N, 13.78.

3-(3-Methylureido)-1-*N*-((*N*′-phthaloyl)methyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (11n). 6% yield: ^{1}H NMR ($CDCl_3$) δ: 1.89–2.03 (1H, m), 2.43–2.79 (3H, m), 2.75 (3H, d, J = 4.6 Hz), 4.36–4.49 (1H, m), 4.42 (1H, d, J = 13.6 Hz), 4.62 (1H, brs), 5.61 (2H, t, J = 8.0 Hz), 6.33 (1H, d, J = 13.6 Hz), 7.13–7.45 (4H, m), 7.67–7.81 (4H, m); HR-FABMS m/z 391.1565 (calcd for $C_{21}H_{21}N_4O_4$ m/z 393.1562).

1-*N*-(3-(*N*′-(*tert*-Butoxycarbonyl)amino)benzyl)-3-methylcarbonylamino-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (12). To a solution of compound **8b** (84 mg, 0.22 mmol) in THF (2 mL) were added Et_3N (0.1 mL, 0.72 mmol) and acetylchloride (50 μL, 0.703 mmol) at 0°C. The mixture was stirred at rt for 15 h and partitioned between EtOAc and water. The aqueous phase was extracted with EtOAc and combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (EtOAc:*n*-hexane = 60:1) to afford **12** (94%): ^{1}H NMR ($CDCl_3$) δ: 1.50 (9H, s), 1.86–1.95 (1H, m), 1.98 (3H, s), 2.46–2.69 (3H, m), 4.48–4.57 (1H, m), 4.95 (1H, d, J = 14.7 Hz), 5.05 (1H, d, J = 15.3 Hz), 6.49 (2H, m), 6.86 (1H, d , J = 7.8 Hz), 7.16–7.25 (5H, m), 7.38 (1H, d, J = 6.9 Hz). Anal. ($C_{29}H_{38}N_4O_4 \cdot 0.2C_6H_{14} \cdot 0.4H_2O$); calcd: C,67.57; H, 7.34; N, 9.38. Found: C, 67.53; H, 8.10; N, 10.84.

Compound **13** was prepared from **8b** according to the same procedure.

1-*N*-(3-(*N*′-(*tert*-Butoxycarbonyl)amino)benzyl)-3-methoxycarbonylamino-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (13). 94% yield: mp 183–184°C; ^{1}H NMR ($CDCl_3$) δ: 1.49 (9H, s), 1.96 (1H, m), 2.46–2.69 (1H, m), 3.36 (1H, s), 4.32 (1H, m), 5.00 (2H, s), 5.66 (1H, brd, J = 7.8 Hz), 6.66 (1H, s), 6.85 (1H, brd, J = 7.5 Hz), 7.12–7.22 (2H, m), 7.45 (1H, d, J = 8.4 Hz). Anal. ($C_{24}H_{29}N_3O_5 \cdot 0.15H_2O$); calcd: C, 65.19; H, 6.68; N, 9.50. Found: C, 65.19; H, 6.74; N, 9.54.

Preparation of 1-*N*-(3-(*N*′-(*tert*-Butoxycarbonylamino)-benzyl)-3-(*N*-phenylguanidino)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (14b)

***S*-Methyl-phenylisothiourea hydroiodide salt.** A suspension of the 1-phenyl-2-thiourea (1.5 g, 9.85 mmol) and MeI (1.25 mL, 20.0 mmol) in CH_3CN (10 mL) was stirred under reflux for 16 h. After cooling, the deposited crystals were collected by filtration and crystallized from Et_2O to give 2.31g (77%) of the target compound: ^{1}H NMR (DMSO) δ: 2.69 (3H, s), 7.30–7.60 (5H, m).

1-*N*-(3-(*N*′-(*tert*-Butoxycarbonyl)amino)benzyl)-3-(*N*-phenylguanidino)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (14b). A mixture of **8b** (382 mg, 1.0 mmol) and *S*-methyl-phenylisothiourea hydroiodide salt (294 mg, 1.0 mmol) in EtOH (1 mL) was heated to 100°C with stirring in a sealed tube for 5 h. After removal of the solvent, EtOAc and 10% aqueous Na_2CO_3 were added to the residue. The EtOAc layer was washed with water, dried over Na_2SO_4, and concentrated in vacuo. The residue was washed with Et_2O, purified by PLC (CH_3CN:MeOH = 3:1), and recrystallized from Et_2O to afforded **47c** (72 mg, 14%) as a crystal: mp 132–135°C; ^{1}H NMR (CD_3OD) δ: 1.49 (9H, s), 2.00 (1H, m), 2.56 (2H, m), 2.69 (1H, m), 4.45 (1H, dd, J = 7.8 Hz, 12.3 Hz), 4.95 (1H, d, J = 15.3 Hz), 5.15 (1H, d, J =

15.3 Hz), 6.85 (1H, d, $J=8.0$ Hz), 6.90–7.10 (5H, m), 7.10–7.40 (7H, m). Anal. ($C_{29}H_{33}N_5O_3\cdot0.5Et_2O$); calcd: C, 69.38; H, 7.14; N, 13.05. Found: C, 69.25; H, 7.10; N, 12.95.

Compounds **14a** and **14c** were prepared from **8b** according to a same procedure.

1-*N*-(3-(*N*′-(*tert*-Butoxycarbonyl)amino)benzyl)-3-(*N*-methylguanidino)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (14a). 34% yield: ^{1}H NMR (CD_3OD) δ: 1.49 (9H, s), 2.14 (1H, m), 2.54 (2H, m), 2.67 (1H, m), 2.81 (3H, s), 4.22 (1H, dd, $J=7.5$ Hz, 12.5 Hz), 4.90 (1H, d, $J=14.6$ Hz), 5.35 (1H, d, $J=14.6$ Hz), 6.81 (1H, d, $J=7.5$ Hz), 7.11 (1H, t, $J=7.2$ Hz), 7.30 (3H, m), 7.40 (3H, m). Anal. ($C_{24}H_{31}N_5O_3\cdot2.0H_2O$); calcd: C, 60.87; H, 7.45; N, 14.79. Found: C, 60.54; H, 7.22; N, 14.89.

1-*N*-(3-(*N*′-(*tert*-Butoxycarbonyl)amino)benzyl)-3-(*N*-(4-hydroxyphenyl)guanidino)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (14c). 17% yield: mp 180–183°C; ^{1}H NMR (CD_3OD) δ: 1.48 (9H, s), 2.05 (1H, m), 2.50–2.80 (3H, m), 4.35 (1H, m), 4.84 (1H, d, $J=14.8$ Hz), 5.30 (1H, d, $J=14.8$ Hz), 6.8 (3H, m), 7.00–7.40 (9H, m). Anal. ($C_{29}H_{33}N_5O_4\cdot0.2EtOAc\cdot2.6H_2O$); calcd: C, 61.65; H, 6.93; N, 11.98. Found: C, 61.69; H, 6.49; N, 12.01.

Preparation of 1-*N*-(3-(*N*′-(*tert*-Butoxycarbonyl)amino)-benzyl)-3-(*N*-methyl-*N*′-phenylguanidino)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (14d)

1-*N*-(3-(*N*′-(*tert*-Butoxycarbonyl)amino)benzyl)-3-(3-phenylthioureido)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one. To a solution of compound **8b** (1.0 g, 2.62 mmol) in CH_3CN (10 mL) was added phenyl isothiocyanate (343 mL, 2.88 mmol) at 0°C and the mixture was stirred at rt for 1 h. The deposited crystals were collected by filtration, washed with Et_2O twice and recrystallized from CH_3CN to obtain the target compound 930 mg (68%) as crystals: mp 132–135°C; ^{1}H NMR (CD_3OD) δ: 1.15 (6H, d, $J=6.3$ Hz), 1.95 (1H, m), 2.50–2.70 (3H, m), 3.86 (1H, m), 4.88 (1H, d, $J=15.0$ Hz), 5.03 (1H, dd, $J=7.2$, 10.1 Hz), 5.17 (1H, d, $J=15.0$ Hz), 6.86 (1H, d, $J=7.5$ Hz), 7.13 (1H, t, $J=8.1$ Hz), 7.20–7.40 (11H, m). Anal. ($C_{29}H_{32}N_4O_3S\cdot0.1CH_3CN$); calcd: C, 67.35; H, 6.25; N, 11.03; S, 6.16. Found C, 67.18; H, 6.29; N, 11.36; S, 6.27.

1-*N*-(3-(*N*′-(*tert*-Butoxycarbonyl)amino)benzyl)-3-(3-(*S*-methyl-phenylisothioureido)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one hydroiodide salt. A suspension of the above thiourea compound (1.0 g, 1.93 mmol) and MeI (0.24 mL, 3.85 mmol) in CH_3CN (3 mL) was stirred at rt for 16 h and then MeI (0.24 mL, 3.85 mmol) was added. The mixture was heated to 40°C with stirring for 2.5 h. After cooling, the reaction mixture was concentrated to afford 290 mg (94%) of the target compound as a foam, which was used directly in the next step: ^{1}H NMR (CD_3OD) δ: 1.15 (6H, d, $J=6.6$ Hz), 2.13 (1H, m), 2.30 (3H, s), 2.40–2.70 (3H, m), 3.85 (1H, m), 4.51 (1H, dd, $J=7.0$, 10.2 Hz), 4.97 (1H, d, $J=15.0$ Hz), 5.08 (1H, d, $J=15.0$ Hz), 6.73 (2H, d, $J=7.5$ Hz), 5.90–7.00 (3H, m), 7.10–7.30 (8H, m).

1-*N*-(3-(*N*′-(*tert*-Butoxycarbonyl)amino)benzyl)-3-(*N*-methyl-*N*′-phenylguanidino)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (14d). To 1-*N*-(3-(*N*′-(*tert*-butoxycarbonyl)amino)benzyl)-3-(3-(*S*-methylphenylisothioureido)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one hydroiodide salt (300 mg, 0.455 mmol) was added 40% methylamine in MeOH solution (1.2 mL) and the mixture was heated to 80°C with stirring in a sealed tube for 4 h. After removal of the solvent, the residue was purified by PLC (1-BuOH:AcOH:H_2O = 5:1:1) to afford **14d** (206 mg, 88%) as a foam: ^{1}H NMR (CD_3OD) δ: 1.48 (9H, s), 2.20 (1H, m), 2.40–2.80 (3H, m), 2.92 (3H, m), 4.31 (1H, dd, $J=7.6$, 11.4 Hz), 4.84 (1H, d, $J=14.8$ Hz), 5.23 (1H, d, $J=14.8$ Hz), 6.80 (2H, d, $J=7.4$ Hz), 7.00–7.40 (12H, m). Anal. ($C_{30}H_{35}N_5O_3\cdot2.3H_2O$); calcd: C, 64.92; H, 6.79; N, 12.80. Found: C, 64.92; H, 7.19; N, 12.62.

Compounds **14e**–**g** were prepared from **8b** according to a similar procedure.

1-*N*-(3-(*N*′-(*tert*-Butoxycarbonyl)amino)benzyl)-3-(*N*-methoxy-*N*′-phenylguanidino)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (14e). 22% yield: ^{1}H NMR (CD_3OD) δ: 1.98 (1H, m), 2.30–2.70 (3H, m), 3.66 (3H, s), 4.10 (1H, m), 4.85 (1H, d, $J=15.0$ Hz), 5.07 (1H, d, $J=15.0$ Hz), 6.80–7.40 (13H, m). Anal. ($C_{30}H_{35}N_5O_4$); calcd: C, 68.03; H, 6.66; N, 13.22. Found: C, 67.84; H, 6.71; N, 13.04.

1-*N*-(3-(*N*′-(*tert*-Butoxycarbonyl)amino)benzyl)-3-(*N*-hydroxy-*N*′-phenylguanidino)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (14f). 27% yield: mp 150–153°C; ^{1}H NMR ($CDCl_3$) δ: 1.50 (9H, s), 1.95 (1H, m), 2.50–2.80 (3H, m), 4.30 (2H, m), 4.70 (1H, d, $J=20.0$ Hz), 5.32 (1H, d, $J=20.0$ Hz), 6.80–7.40 (13H, m). Anal. ($C_{29}H_{33}N_5O_4\cdot0.2Et_2O$); calcd: C, 67.65; H, 6.63; N, 13.00. Found: C, 67.84; H, 6.65; N, 13.20.

1-*N*-(3-(*N*′-(*tert*-Butoxycarbonyl)amino)benzyl)-3-(*N*,*N*′-dimethyl-*N*″-phenyl)guanidino)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (14g). 43% yield: ^{1}H NMR (CD_3OD) δ: 1.49 (9H, s), 1.95 (1H, m), 2.15 (1H, m), 2.34 (1H, m), 2.52 (1H, m), 2.89 (6H, s), 3.99 (1H, dd, $J=7.5$, 11.5 Hz), 4.77 (1H, d, $J=15.0$ Hz), 5.09 (1H, d, $J=15.0$ Hz), 6.61 (2H, d, $J=7.2$ Hz), 6.69 (2H, d, $J=7.2$ Hz), 6.77 (1H, d, $J=7.2$ Hz), 6.90–7.30 (9H, m). Anal. ($C_{29}H_{33}N_5O_4\cdot0.2H_2O$); calcd: C, 70.09; H, 7.10; N, 13.18. Found: C, 70.03; H, 7.12; N, 13.00.

Preparation of 5-*N*-(3-(*N*′-(*tert*-butoxycarbonyl)amino)-benzyl)-3-(3-phenylureido)-2,3-dihydro-5*H*-1,5-benzothiazepin-4-one (16)

3-Phenylureido-2,3-dihydro-5*H*-1,5-benzothiazepin-4-one. A mixture of 3-phthalimido-2,3-dihydro-5*H*-1,5-benzothiazepin-4-one (250 mg, 0.77 mmol) and hydrazine monohydrate (119 mg) in EtOH (8.5 mL) was stirred under reflux for 1 h. After cooling, the reaction mixture was partitioned between EtOAc and H_2O. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was washed with *n*-hexane and no further purification was done. The

resulting amine was *N*-alkylated by the procedure according to Method B to give the target compound in 59% yield: mp 233°C (dec.) ^{1}H NMR ($CDCl_3$ + CD_3OD) δ: 2.73 (3H, brs), 2.95 (1H, t, J = 10.2 Hz), 3.85 (1H, dd, J = 6.6 Hz, 11.0 Hz), 4.69 (1H, m), 6.23 (1H, m), 6.96–7.38 (10H, m), 7.65 (1H, d, J = 6.2 Hz). Anal. ($C_{16}H_{15}N_3O_2S \cdot 0.1H_2O$); calcd: C, 60.97; H, 4.86; N, 13.33; S, 10.17. Found: C, 61.16; H, 4.86; N, 13.41; S, 9.93.

5-*N*-(3-(*N*′-(*tert*-Butoxycarbonyl)amino)benzyl)-3-(3-phenylureido)-2,3-dihydro-5*H*-1,5-benzothiazepin-4-one (16). This compound was prepared according to Method A from compound **4** and 3-phenylureido-2,3-dihydro-5*H*-1,5-benzothiazepin-4-one in 56% yield: ^{1}H NMR ($CDCl_3$) δ: 1.49 (9H, s), 2.92 (1H, t, J = 11.5 Hz), 3.79 (1H, dd, J = 6.8 Hz, 11.2 Hz), 4.79 (2H, m), 4.89 (1H, d, J = 15.6 Hz), 5.26 (1H, d, J = 16.2 Hz), 6.65 (2H, brs), 6.95 (2H, m), 7.08–7.26 (8H, m), 7.30–7.45 (2H, m), 7.46 (1H, d, J = 7.8 Hz). Anal. ($C_{26}H_{34}N_4O_6S \cdot 0.1C_6H_{14}$); calcd: C, 65.15; H, 6.00; N, 10.63; S, 6.08. Found: C, 65.22; H, 6.14; N, 10.69; S, 6.01.

5-*N*-(3-(*N*′-(*tert*-Butoxycarbonyl)amino)benzyl)-3-(3-phenylureido)-2,3-dihydro-5*H*-1,5-benzoxazepin-4-one (18) was prepared according to Method A from compound **4** and 3-benzyloxycarbonylamino-2,3-dihydro-5*H*-1,5-benzothiazepin-4-one, followed by removal of the Cbz group by hydrogenolysis using 5% Pd-C. The resulting amine was converted to the target compound according to Method B using phenylisocyanate (37% yield): ^{1}H NMR (CD_3OD) δ: 1.48 (9H, s), 4.30 (1H, m), 4.55 (1H, m), 4.89 (1H, dd, J = 7.8 Hz, 11.4 Hz), 4.97 (1H, d, J = 15.9 Hz), 5.24 (1H, d, J = 15.9 Hz), 6.90 (2H, m), 7.10–7.40 (11H, m). Anal. ($C_{28}H_{30}N_4O_5 \cdot 0.5H_2O$); calcd: C, 65.74; H, 6.11; N, 10.95. Found: C, 65.87; H, 6.10; N, 10.88.

NPY Receptor Binding Assay

NPY Y1 and Y2 receptor binding assays were conducted as described previously[27,28] with minor modification. [^{125}I]PYY (DuPont-New England Nuclear) was used as the radioligand for NPY receptors instead of [^{125}I]NPY because the former nonspecific binding was lower than the latter. SK-N-MC and SMS-KAN cells were cultured in 12-well culture plates for Y1 and Y2 receptor binding assays, respectively. After 2 days, the medium was removed and the cells were washed with HEPES (20 mM)-buffered Hank's solution (pH 7.4) containing 1% bovine serum albumin (binding buffer). For competitive binding experiments, the cells were incubated with 0.1 nM [^{125}I]PYY and varying concentrations of unlabeled compounds in 0.5 mL of binding buffer at 37°C for 60 min. For Scatchard plot analysis, the cells were incubated with 0.02–0.4 nM [^{125}I]PYY. The incubation was stopped by removing the assay mixture and the cells were washed twice with 1 mL of ice-cold binding buffer, lysed with 1.5 mL of 1 N NaOH and transferred to test tubes. The radioactivity was counted with a γ counter. Nonspecific binding was determined in the presence of 10^{-6} M NPY. NPY Y5 receptor binding was carried out using membranes from CHO cells expressing cloned human NPY Y5, as described previously.[29] Cytosolic free Ca^{2+} concentration in SK-N-MC cells was measured fluorometrically using the Ca^{2+}-sensitive fluorescent dye fura-2 with a spectrofluorometer (CAF-100, Japan Spectroscopy Inc., Tokyo, Japan) as described previously.[27]

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