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

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A novel series of potent and selective non-peptide neuropeptide Y (NPY) Y1 receptor antagonists, having benzazepine nuclei, have been designed, synthesized, and evaluated for activity. Chemical modification of the R_1 and R_3 substituents in structure **1** (Chart 1) yields several compounds that show high affinity for the Y1 receptor (K_i values of less than 10 nM). SAR studies revealed that introduction of an isopropylurea group at R_1 and a 3-(benzo-condensed-urea) group, 3-(fluorophenylurea) group, or a 3-(*N*-(4-hydroxyphenyl)guanidine) group at R_3 in structure **1** afforded potent and subtype-selective NPY Y1 receptor antagonists. 3-(3-(Benzothiazol-6-yl)ureido)-1-*N*-(3-(*N*-(3-isopropylureido))benzyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (**21**), which was one of the most potent derivatives, competitively inhibited specific [^{125}I]peptide YY (PYY) binding to Y1 receptors in human neuroblastoma SK-N-MC cells (K_i = 5.1 nM). **21** not only inhibited the Y1 receptor-mediated increase in cytosolic free Ca^{2+} concentration in SK-N-MC cells but also antagonized the Y1 receptor-mediated inhibitory effect of peptide YY on gastrin-induced histamine release in rat enterochromaffin-like cells. **21** showed no significant affinity in 17 receptor binding assays including Y2, Y4, and Y5 receptors.

Introduction

Neuropeptide Y (NPY), a 36-amino acid peptide, was first isolated from porcine brain tissue in 1982 by Tatemoto et al.[1] NPY is widely distributed in the central and peripheral nervous systems in many mammalian species including humans and belongs to a family of biologically active polypeptides such as peptide YY (PYY) and pancreatic polypeptide (PP). The tertiary structure of NPY was characterized by X-ray studies,[2] molecular dynamics simulation, and spectral studies[3−5] as a poly(proline) type II helix for residues 1−8, a β-turn through positions 9−14, an amphipathic α-helix segment for residues 15−32, and a nonstructured C-terminus for residues 33−36. NPY has been demonstrated to be involved in numerous physiological responses, such as cardiovascular regulation, food intake, energy regulation, pain, and anxiety via its specific receptors.[6,7]

In human tissues, four receptor subtypes for NPY (Y1, Y2, Y4, and Y5) have been identified and revealed to belong to the seven-transmembrane receptor superfamily.[6−8] The Y1 receptor was cloned and sequenced in 1992,[9] the Y2 receptor[10] and the Y4/PP1 receptor[11] in 1995, and the Y5 receptor in 1996.[12] The best characterized is the Y1 receptor, defined as having high and equal affinity for NPY and PYY but low affinity for PP and C-terminal fragments of NPY/PYY.[6,7] In the cardiovascular system, Y1 receptors in vascular smooth muscle cells are suggested to mediate long-lasting vasoconstriction. In the gastrointestinal tract, PYY is reported to be involved in inhibition of gastric acid secretion, pancreatic exocrine secretion, and gastrointestinal motility via Y1 receptors. In the central nervous system, the Y1 receptor appears to be involved in the anxiolytic effects of centrally administered NPY. In addition, NPY produces dramatic increases in food intake via Y1-like receptors.[13] The recently cloned Y5 receptor is thought to be the long-awaited Y1-like receptor involved in feeding behavior,[12] but the Y1 receptor also seems to play some role in food intake because the orexigenic effects of NPY observed in Y5-deficient mice were shown to be completely abolished by the peptidic Y1 antagonist 1229U91.[14] Thus blockade of the Y1 receptor may be used in treating congestive heart failure, angina pectoris, hypertension, digestive function disorder, and obesity.

In the past few years, some non-peptide NPY Y1 receptor antagonists, such as BIBP3226 (K_i = 7.2 nM), SR120819A (K_i = 15 nM), PD160170 (K_i = 48 nM), and LY-357897 (K_i = 0.75 nM), have been reported.[6,15,16] Also in our laboratories, a benzodiazepine derivative was found to have potent Y1 antagonist activities.[17] In a previous study,[18] we synthesized compounds **B** (K_i = 160 nM) and **C** (K_i = 39 nM) with moderate binding affinity from chemical modification of **A** (K_i = 1.5 μM) (Chart 1), which was found to be active by blind screening. In this paper, we report further optimization of these compounds and the discovery of a series of novel, highly potent, selective NPY Y1 receptor antagonists.

Chemistry

3-Aminobenzyl alcohol **2** was converted to urea and then mesylated, followed by reaction with LiBr to give benzyl bromide derivative **4** (Scheme 1). *N*-Alkylation of 3-azidobenzazepine **5**[19] was achieved by reaction with 3-*N*-(*tert*-butoxycarbonyl)aminobenzyl bromide which was prepared by a literature procedure[20] from **2** or compound **4** under phase-transfer conditions (method A), and then the azide group was reduced to amino

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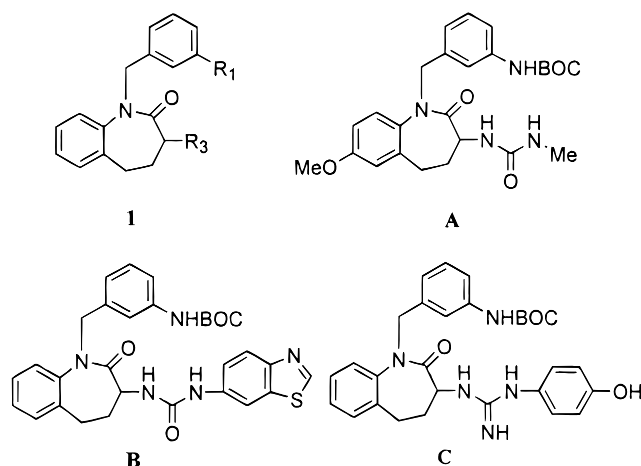
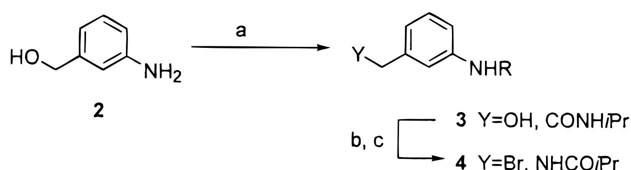
Chart 1. General Formula **1** and Chemical Structures of **A**, **B**, and **C**



Scheme 1[a]



[a] Reagents: (a) *i*PrNCO; (b) MsCl, Et_3N, DMF; (c) LiBr, DMF.

compounds **6a**,**b** by the catalytic hydrogenolysis over palladium on carbon. The amino compounds **6a**,**b** were treated with isocyanates or carbonyldiimidazole followed by amines to give urea derivatives **7** and **8**−**40** (methods B, C). Amine **6b** was converted to guanidine derivatives **41a**−**e** by the reaction with isocyanate compounds, followed by methylation at the sulfur position and then treatment with amines (method D), as shown in Scheme 2.

The BOC group of **7** was removed with trifluoroacetic acid to give **42**, which was converted to carbamate derivatives **43a**−**c** by treatment with chloroformates or to urea derivatives **44a**−**g** or **45** by method B described as above (Scheme 3).

The azide compound **5** was *N*-alkylated with 3-*N*-(*tert*-butoxycarbonyl)aminobenzyl alcohol and then methylated at the nitrogen of a BOC-amino group. The azide group at the C-3 position was converted to a phenylurea group by the same method as described previously to give **46**. Compound **5** was also *N*-alkylated with **4**, and the azide group was reduced to an amino group, which was converted to sulfonamide derivative **47** or carbamate compound **48**, as shown in Scheme 4. The hydroxyl compound, which was easily prepared[21] from the chloride **49**,[19] was then *N*-alkylated with **4**, followed by treatment with phenyl isocyanate to give **50**. Replacement of the chloride of **49** with a cyano group was achieved with KCN in DMF. Next, the cyano group of **51** was hydrogenated catalytically in an acidic condition to give an amino compound, which was treated with phenyl isocyanate to give urea compound **52**. The cyano group of **51** was hydrolyzed with 10% HCl−MeOH to the carboxylic acid **53**, which was then reduced with $LiBH_4$ to the alcohol via the methyl ester. The alcohol was treated with phenyl isocyanate to obtain **54**. Also the carboxylic acid of **53** was converted to amide compound **55** by a coupling method with aniline.

Dimethyl isophthalate (**56**) was hydrolyzed to the half-ester, which was converted to the next higher homologue by Arndt−Aistert synthesis and then treated with oxalyl chloride and *i*$PrNH_2$ to afford amide **57** (Scheme 5). The ester group of **57** was reduced to the alcohol, which was then brominated with triphenylphosphine and NBS to give the bromide **58**. Compound **5** was *N*-alkylated with **58** by the same procedure cited above to give **59**.

3-Amino-ϵ-caprolactam (**60**) was first treated with phenyl isocyanate to give a urea compound, which was then *N*-alkylated with **4** and NaH to give **61** (Scheme 6). 3-*N*-BOC-aminobenzoxazepine (**62**)[22] was *N*-alkylated as above, and after removal of the BOC group, the amino compound was converted to the urea derivative **63** (Scheme 7).

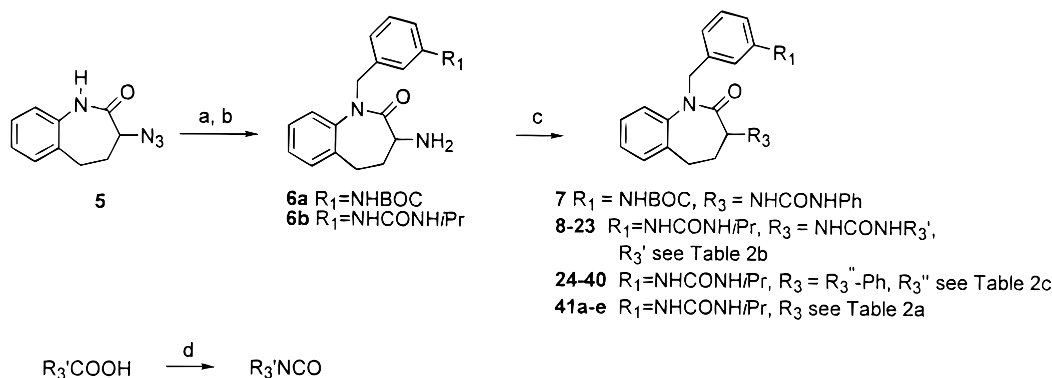
3-Azido-3,4,5,6-tetrahydro-1*H*-1-benzazocin-2-one (**65**), which was prepared according to the same procedure in the literature[23] from 3,4,5,6-tetrahydro-1*H*-1-benzazocin-2-one (**64**),[24] was treated with the same method used for the preparation of **7** to give **66** (Scheme 8). 2-Amino-4-(hydroxymethyl)thiazole (**67**)[25] was treated with isopropyl isocyanate to give urea derivative **68**, which was converted to bromide **69** (Scheme 9). 3-Aminobenzazepine (**70**) was *N*-alkylated with **69**, and then the product was treated by the same procedure described in Scheme 2 to give **71**.

Results 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 human neuroblastoma SK-N-MC cells. To find antagonists more active than **A** or **B**,[18] two positions for the R_1 and R_3 substituents of **1** (Chart 1) were selected for further chemical modification.

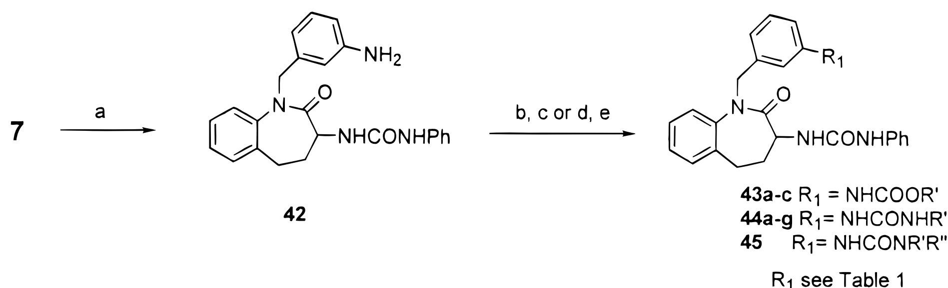
Since aromatic substituents at urea are favorable for the NPY Y1 binding affinity,[18] the R_3 position of the benzazepine system was fixed with the phenylurea moiety to carry out the chemical modification at position R_1 (Table 1). Urea derivatives in general were less potent than guanidine derivatives but more suited for chemical modifications because of greater stability under most chemical reactions. First of all, we introduced carbamate and urea residues to position R_1. Several modifications revealed that the sequences of potency were *i*Pr $\geq$ *t*Bu > Me, Ph (**7**, **43a**−**c**) in the case of carbamate derivatives and *i*Pr > *i*Bu > *t*Bu > cyclopropyl > Me $\gg$ H, Ph (**44a**−**g**) in the case of urea derivatives. In two series of substituents at the R_1 position, carbamate derivatives were more potent in binding affinity than urea derivatives. For example, **43b** (*i*Pr carbamate) showed higher affinity than **44d** (*i*Pr urea). Also, these data indicate that an alkyl group of appropriate size is suitable as the residue introduced to urea or carbamate at R_1. *i*Pr showed the highest affinity. Only the size did not appear to be important, since the phenyl group was not tolerated at all, as was seen with **44g**. The existence of π-electron may hinder the interaction with the receptor. The replacement of −NH− adjacent to the benzene ring with $-CH_2-$ was detrimental to activity (**44d** vs **59**). Since the *N*-methylated BOC compound **46** lost its affinity, the

Scheme 2[a]



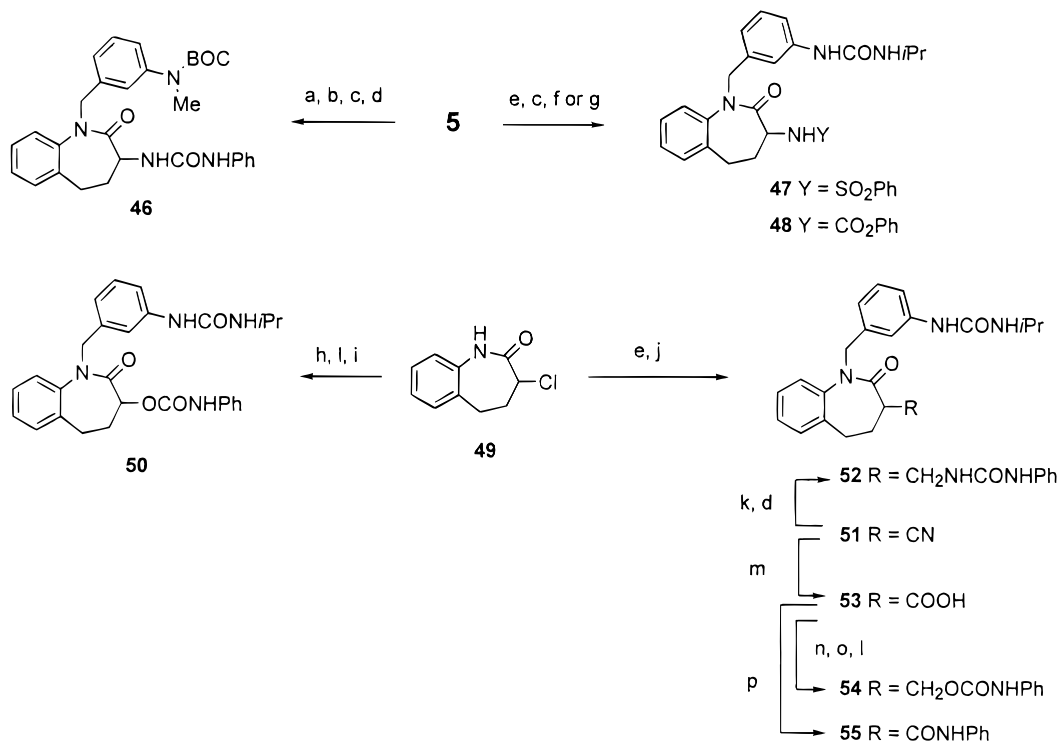
[a] Reagents: (a) 3-*N*-Boc-aminobenzyl alcohol or **4**, KOH, $nBu_4N^+Br^-$, THF (method A); (b) H_2, 10% Pd−C, MeOH; (c) (method B) R_3NCO; (method C) 1. Imd_2CO, CH_3CN, 2. amines; or (method D) (i) R′NCS, (ii) 1. CH_3I, 2. K_2CO_3, EtOH, (iii) amines; (d) 1. $SOCl_2$, NaN_3, 2. Δ, toluene.

Scheme 3[a]



[a] Reagents: (a) TFA, CH_2Cl_2, anisole; (b) R′OCOCl, Et_3N, THF; (c) $Cl_3CCONCO$, toluene, $NaHCO_3$(aq); (d) method B; (e) R′R″NCOCl, Et_3N, CH_2Cl_2.

Scheme 4[a]

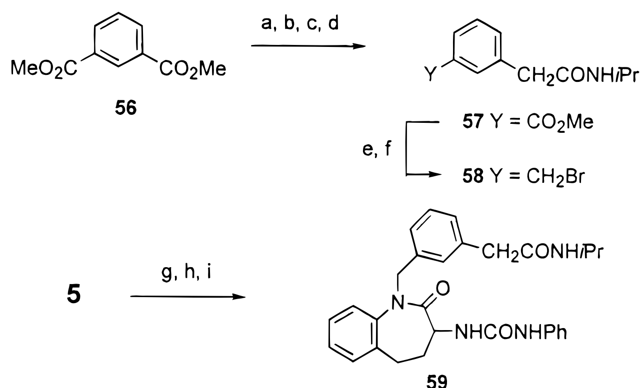


[a] Reagents: (a) method A; (b) NaH, MeI; (c) H_2, 10% Pd−C, MeOH; (d) PhNCO; (e) method A; (f) $ClSO_2Ph$; (g) PhOCOCl; (h) 1. HCOOH, TEA, 2. HCl−MeOH; (i) NaH, **4**; (j) KCN, $nBuN^+Br^-$, DMSO; (k) H_2, 10% Pd-C, HCl/EtOH; (l) PhNCO, cat. $(nBu_3Sn)_2O$; (m) 1.10% HCl−MeOH, 2. NaOH(aq); (n) CH_2N_2; (o) $LiBH_4$, THF; (p) aniline, WSCD, HOBT, THF.

hydrogen of −NHCO− bound to the benzene ring at R_1 may be necessary for the hydrogen bond with the receptor.

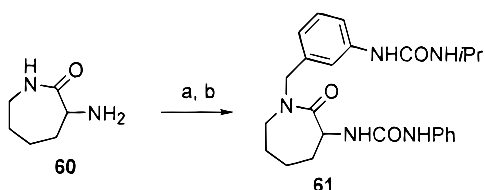
Next, since **44d** was the most potent compound in the variations at R_1, we fixed R_1 as *i*Pr urea to optimize the position R_3 of the benzazepine system again (Table 2).

Scheme 5[a]



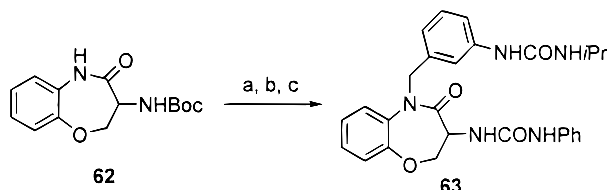
[a] Reagents: (a) NaOH, MeOH; (b) 1. $SOCl_2$, 2. CH_2N_2; (c) Ag_2O, 1,4-dioxane; (d) 1. $(COCl)_2$, 2. *i*$PrNH_2$, toluene; (e) $LiBH_4$; (f) NBS, PPh_3, THF; (g) **58**, method A; (h) H_2, 10% Pd−C, MeOH; (i) PhNCO.

Scheme 6[a]



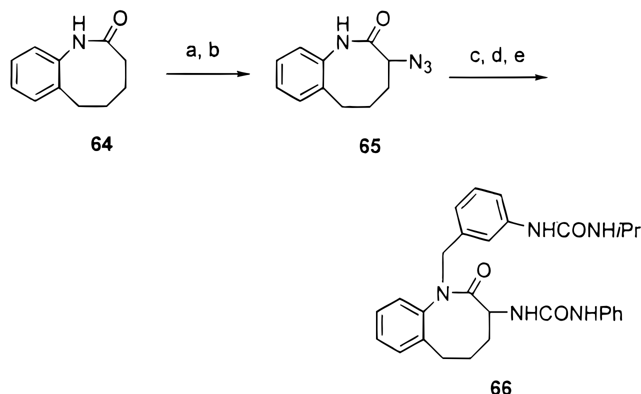
[a] Reagents: (a) PhNCO; (b) NaH, **4**, DMF.

Scheme 7[a]



[a] Reagents: (a) **4**, method A; (b) 4 N HCl−EtOAc; (c) PhNCO.

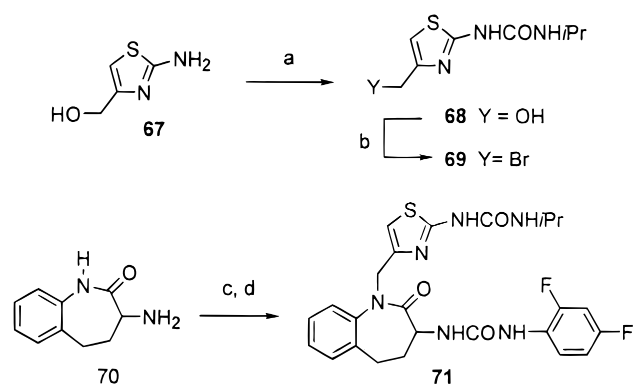
Scheme 8[a]



[a] Reagents: (a) Br_2, PCl_5; (b) NaN_3; (c) **4**, method A; (d) H_2, 10% Pd−C, MeOH; (e) PhNCO.

Replacement of the urea moiety (−NHCONHPh) with a sulfonamide moiety ($-NHSO_2Ph$) or carbamate moieties (−NHCOOPh and −OCONHPh) resulted in decreases in binding affinity of 1−2 orders of magnitude (**44d** vs **47**, **48**, **50**). Substitution with an amide moiety (−NHCOPh) led to the inactive compound **55**. The insertion of a methylene spacer resulted in approximately 10-fold drops in binding affinity (**52** vs **44d** and **54** vs **50**). Introduction of a guanidine moiety resulted in 3-fold higher binding affinity (**41a** vs **44d**). These findings imply that not only the distance between the benzene ring and the benzazepine nucleus but also the bond style of the position R_3 is important for the interaction with the Y1 receptor. Introduction of the 4-hydroxy group to the phenyl group enhanced the binding affinity by about 2-fold (**41c** vs **41a**). This may be related to the reported importance of Tyr^1 and Tyr^{36} of NPY for the interaction with the Y1 receptor.[26] **41b** was the most potent compound of **41b** and its *N*-alkylated compounds (**41c**−**e**). The hydroxyethyl substituent **41d** was the weakest, although it still showed moderate affinity. The hydrophilic group may not be profitable to the receptor−ligand interaction.

Scheme 9[a]



[a] Reagents: (a) *i*PrNCO; (b) NBS, PPh_3, THF; (c) (2,4-F_2)-C_6H_3NCO; (e) *n*BuLi, **69**, THF.

Table 1. In Vitro NPY Y1 Receptor Binding Affinity (**42**, **43a**−**c**, **44a**−**g**, **45**, **46**, and **59**)

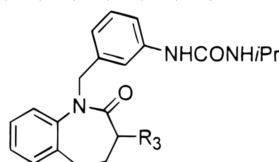
compd	R_1	K_i (μM)[a]
7	NHCOO*t*Bu	1.2
42	NH_2	>10
43a	NHCOOMe	>10
43b	NHCOO*i*Pr	0.69
43c	NHCOOPh	>10
44a	$NHCONH_2$	>10
44b	NHCONHMe	7.3
44c	NHCONH-cyclopropyl	0.91
44d	NHCONH*i*Pr	0.043
44e	NHCONH*i*Bu	0.075
44f	NHCONH*t*Bu	0.14
44g	NHCONHPh	>10
45	NHCO-morpholinyl	>10
46	N(Me)COO*t*Bu	>10
59	CH_2CONH*i*Pr	3.8

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

We explored and evaluated the effect of the introduction of heteroaromatic groups on urea substituents (**8**−**23**). In these heteroaromatic series, the sequence of potency for displacing [^{125}I]PYY binding was as follows: 6-benzothiazolyl > 5-benzoxazolyl = 5-indolyl ≥ 5-indazolyl > phenyl > 6-quinolinyl ≥ 4-pyridinyl ≥ 3-quinolinyl = 2-thiadiazolyl = 2-thiazolyl ≥ 2-pyradinyl > 3-pyrazolyl. These results suggest that the benzene

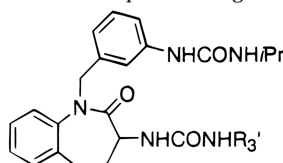
Table 2

a. In Vitro NPY Y1 Receptor Binding Affinity (**44d**, **47**, **49**, **50**, **52**, **54**, **55**, and **41a**−**e**)



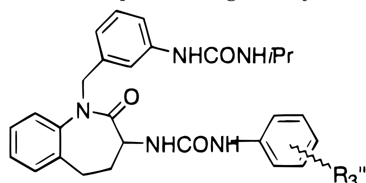
compd	R_3	K_i (nM)[a]
44d	NHCONH*i*Pr	43
47	$NHSO_2Ph$	5500
48	NHCOOPh	2100
50	OCONHPh	450
52	$CH_2NHCONHPh$	1400
54	$CH_2OCONHPh$	4100
55	NHCOPh	>10000
41a	NHC(−NHMe)=NPh	15
41b	$NHC(-NH_2)=NC_6H_4(4\text{-}OH)$	2.9
41c	$NHC(-NHMe)=NC_6H_4(4\text{-}OH)$	7.3
41d	$NHC(-NH(CH_2CH_2OH))=NC_6H_4(4\text{-}OH)$	65
41e	NHC(−NH*i*Pr)=$NC_6H_4(4\text{-}OH)$	36

b. In Vitro NPY Y1 Receptor Binding Affinity (**8**−**23**)



compd	R_3'	K_i (nM)[a]
8	4-pyridinyl	83
9	2-pyradinyl	240
10	3-pyrazolyl	>10000
11	2-thiazolyl	160
12	1,3,4-thiadiazolyl	150
13	5-indolyl	18
14	6-benzofuryl	7.8
15	5-benzothienyl	13
16	6-benzothienyl	7.8
17	3-quinolinyl	140
18	6-quinolinyl	56
19	2-benzothiazolyl	690
20	5-benzothiazolyl	24
21	6-benzothiazolyl	5.1
22	5-indazolyl	26
23	5-benzoxazolyl	17

c. In Vitro NPY Y1 Receptor Binding Affinity (**44d** and **24**−**40**)



compd	R_3''	K_i (nM)[a]
44d	H	43
24	4-OH	82
25	4-F	29
26	4-Cl	71
27	$4\text{-}NO_2$	88
28	$4\text{-}NMe_2$	66
29	4-Ph	610
30	4-OMe	80
31	$4\text{-}NH_2$	200
32	2-F	7.6
33	$2,3\text{-}F_2$	100
34	$2,4\text{-}F_2$	7.8
35	$3,5\text{-}F_2$	86
36	$3,4\text{-}(OCH_2O)-$	28
37	$3,4\text{-}(OCH_2CH_2O)-$	18
38	$3,4\text{-}(CH_2CH_2CH_2)-$	17
39	3,4-(CONHCO)−	25
40	3,4-(CON(Me)CO)−	780

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

Table 3. In Vitro NPY Y1 Receptor Binding Affinity (**61**, **64**, **66**, and **71**)

compd	K_i (nM)[a]
61	7000
63	470
66	56
71	>10000

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

ring of the benzo-condensed ring is important for the binding affinity (**10** vs **22**), that the benzene ring connected directly with the ureido nitrogen would be better than those connected indirectly (**17** vs **18**, **19** vs **20** and **21**), and that the position of the benzene ring connected with the ureido nitrogen is important for binding affinity (**20** vs **21**).

Although introduction of substituting groups on the ureidobenzene ring did not influence or reduce the binding affinity in general, only 2-fluoro- and 2,4-difluoro-substituted compounds **32** and **34**, respectively, showed higher affinities than the nonsubstituted compound **44d**. Not the electronic effect of the substituting groups, such as electron-donating or -withdrawing, but their bulkiness may be a factor influencing the binding affinity as seen in compounds **24**−**31**. 3,4-Cyclized phenyl compounds **36**−**39**, except the *N*-methylated compound **40**, were a little more potent than **44d**. Excessive bulkiness may not be beneficial for the interaction with the receptor.

Other modifications were not tolerated, such as elimination of the benzene ring of the benzazepine yielding the lactam ring system (**61**) and introduction of an oxygen atom into the lactam ring (**63**). Expansion of the lactam ring size did not result in significant change in binding affinity (**66** vs **44d**). Also replacement of the benzyl group at R_1 with a 4-thiazolylmethyl group produced the inactive compound **71**.

To assess the Y1 selectivity of this series of compounds, we selected 13 compounds with high affinity for Y1 receptors from Table 2 (**13**−**16, 21, 23, 32, 34, 37, 38,** and **41a**−**c**: $K_i \leq 18$ nM), 2 compounds from Table 1 (**44e**,**f**), and 1 compound from Table 3 (**66**) and measured their affinities for Y2 and Y5 receptors. None of the compounds had affinity for either of them (K_i > 10 000 nM). These compounds also showed no affinity for Y4 receptors (K_i > 10 000 nM). Although it was reported that a peptide Y1 receptor antagonist, 1229U91 and related peptides, show Y4 receptor agonist activity,[27,28] non-peptide Y1 antagonists might not able to interact with Y4 receptors.

Further characterization of this series of compounds was performed with **21**. The affinity of **21** was close to that of NPY or BIBP3226, a well-known Y1 antagonist, as shown in Figure 1A. Scatchard plot analysis revealed that the presence of **21** changed only the K_d value of $[^{125}I]$PYY binding without alteration of the maximal binding (Figure 1B), suggesting apparently competitive antagonism. The NPY Y1 receptor, as well as other NPY receptor subtypes, belongs to the seven-transmembrane G-protein-coupled receptor superfamily. **21** did not show any effects on Y2, Y4, and Y5 receptor bindings or on those of other members of the seven-transmembrane G-protein-coupled receptor family, for example, endothelins ET-A and ET-B, bombesin, angiotensins AT1

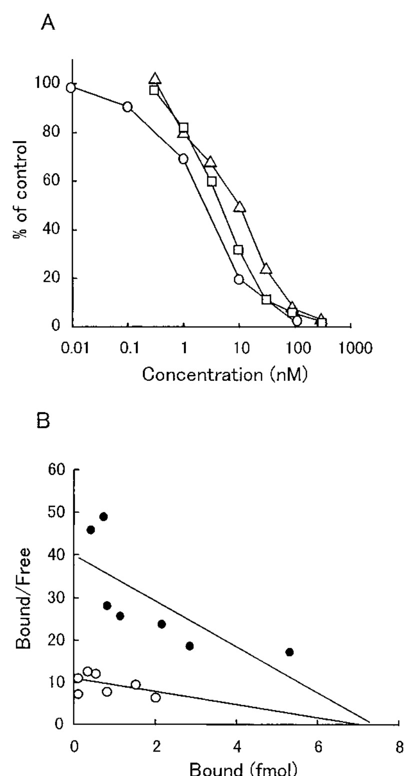


Figure 1. (A) Effect of NPY (○), **21** (□), and BIBP3226 (△) on the [^{125}I]PYY binding to SK-N-MC cells. Symbols represent the mean values of duplicate determinations and are representative of those from three separate experiments. (B) Scatchard plot analysis of the [^{125}I]PYY binding to SK-N-MC cells in the absence (●) or presence (○) of 100 nM **21**. The plot was transformed from the saturation curve of the specific binding.

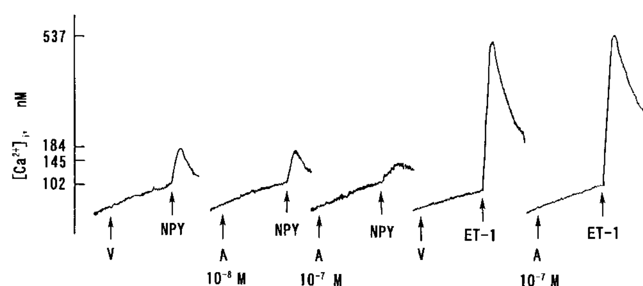


Figure 2. Effect of **21** on antagonist-induced increases in cytosolic free Ca^{2+} concentration ($[Ca^{2+}]_i$) in SK-N-MC cells. Cells were stimulated by 10^{-7} M NPY or 10^{-7} M endothelin-1 (ET-1). **21** (A) and dimethyl sulfoxide (V) were added 2 min before the stimulation. The traces were obtained from one experiment but are representative of three separate experiments.

and AT2, bradykinins B1 and B2, cholecystokinins A and B, calcitonin-gene-related peptide, tachykinin NK1, and opiate-δ, -κ, and -μ receptors. In addition to the binding profile, functional activities of **21** were examined using two types of living cells, SK-N-MC cells and rat enterochromaffin-like (ECL) cells, both of which have functional Y1 receptors.[17,29] First, **21** dose-dependently inhibited the NPY-induced, but not the endothelin-1-induced, increase in cytosolic free Ca^{2+} concentration in SK-N-MC cells (Figure 2). **21** had no effect on basal cytosolic free Ca^{2+} levels, indicating it has no agonist activity. Eight other selected compounds (**15**, **21**, **32**, **38**, **41b**, **44e**,**f**, and **66**) also scarcely affected the basal Ca^{2+} level but inhibited NPY-induced Ca^{2+} mobilization. The

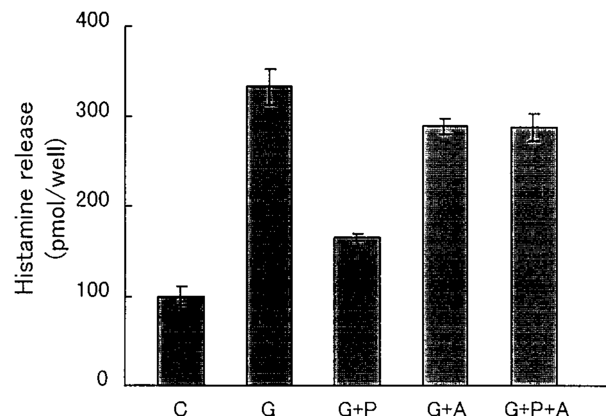


Figure 3. Effect of **21** on the inhibition by PYY of gastrin-17-stimulated histamine release from the ECL cell-enriched fraction. Cells were stimulated by 5×10^{-9} M gastrin-17 (G) with or without 1×10^{-8} M PYY (P). **21** (A; 2×10^{-6} M) was added 30 min before the stimulation. Data represent the released histamine content and are presented as the mean ± SE from four experiments.

property of **21** as a Y1 antagonist was confirmed by another study with ECL cells. PYY partially, but not completely, inhibited the gastrin-evoked histamine release from ECL cells. **21** antagonized this inhibitory effect of PYY on the histamine release (Figure 3). These results of the functional experiments suggested that this series of compounds including **21** are Y1 receptor-specific antagonists.

Conclusion

We have discovered novel 1,3-disubstituted 2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-ones to be potent and selective NPY Y1 receptor antagonists. SAR studies revealed that introduction of an isopropylurea group at R_1 and a 3-(benzo-condensed-urea) group, 3-(fluorophenylurea) group, or 3-(*N*-(4-hydroxyphenyl)guanidine) group at R_3 in structure **1** (Chart 1) afforded potent and subtype-selective NPY Y1 receptor antagonists, seven compounds of which showed K_i values of less than 10 nM. Unfortunately, there still remain some unsolved issues with regard to the solubility of these compounds in aqueous solution and oral bioavailability; further in vivo evaluation of this antagonist has not been performed. However, their novel and unique structure should offer much information useful for not only the analysis of the binding pocket of the NPY Y1 receptor but also the exploration of clinically effective NPY Y1 receptor antagonists.

Experimental Section

General Methods. Melting points are not corrected. ^{1}H NMR spectra were recorded on Varian VXR-200 and VXR-300 FT ^{1}H NMR spectrometers 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 plates (0.5-mm thickness). All reactions were carried out under nitrogen atmosphere with anhydrous solvents that had been dried over 4-Å molecular sieves.

The following compounds were prepared by the literature methods: 5-benzothiazolamine,[30] 6-benzothiazolamine,[31] 5-benzoxazolamine,[32] benzo[*b*]thiophen-5-amine,[33] benzo[*b*]thiophen-

6-amine,[34] 6-nitrobenzofuran,[35] benzo[*b*]thiophene-5-carboxylic acid,[36] and benzo[*b*]thiophene-6-carboxylic acid.[36]

3-(*N*-(Isopropylureido))benzyl Alcohol (3). To a solution of 3-aminobenzyl alcohol (25 g, 203 mmol) in CH_3CN (45 mL) was added a solution of isopropyl isocyanate (23 mL, 201 mmol) in CH_3CN (60 mL) at 0 °C. The mixture was stirred at room temperature for 30 min and at 50 °C for 2.5 h. EtOAc (300 mL) was added, the reaction mixture was allowed to stand for 30 min, and the deposited solid was collected. Trituration with ether afforded **3** (35.3 g, 84%) as crystals, which were used directly in the next step: mp 144−145 °C; ^{1}H NMR (CD_3OD) δ 1.17 (6H, d, J = 6.6 Hz), 3.88 (1H, m, J = 6.6 Hz), 4.55 (2H, s), 6.96 (1H, d, J = 6.9 Hz), 7.24 (2H, m), 7.32 (1H, s). Anal. ($C_{11}H_{16}N_2O_2$) C, H, N.

3-(*N*-(Isopropylureido))benzyl Bromide (4). To a solution of compound **3** (2.34 g, 11.2 mmol) in DMF (23 mL) were added triethylamine (Et_3N) (2.04 mL, 14.6 mmol) and methanesulfonyl chloride (1.13 mL 14.6 mmol) at 0 °C. After the mixture was stirred at room temperature for 1 h, it was 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 crystallized from ether to give the mesylate compound (2.66 g, 93%). To a solution of the mesylate compound (2.60 g, 9.1 mmol) in DMF (20 mL) was added lithium bromide (1.21 g, 13.9 mmol) at 0 °C. The mixture was stirred at same temperature for 1.3 h. The same workup and purification was done to give **5** (2.38 g, 80% from **3**) as crystals: mp 162−165 °C; ^{1}H NMR (CD_3OD) δ 1.17 (6H, d, J = 6.6 Hz), 3.88 (1H, m, J = 6.6 Hz), 4.50 (2H, s), 7.01 (1H, m), 7.23 (2H, m), 7.45 (1H, m). Anal. ($C_{11}H_{15}N_2OBr$) C, H, N, Br.

Method A. Preparation of 3-Azido-1-*N*-(3-*N*-(*tert*-butoxycarbonyl)aminobenzyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one. A suspension of 3-*N*-(*tert*-butoxycarbonyl)-aminobenzyl bromide[25] (3.26 g, 11.4 mmol), **5** (2.0 g, 9.89 mmol), and tetra-*n*-butylammonium 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 room temperature for 2 h. The reaction mixture was neutralized by 0.5 N HCl and extracted with EtOAc. The organic extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (Et_2O/*n*-hexane = 1/2) to afford 3.80 g (96%) of the title 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)aminobenzyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (6a). 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 room temperature overnight. After removal of the catalyst by filtration, the filtrate was evaporated to dryness to give **6a** (4.09 g, quantitative) 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. ($C_{22}H_{27}N_3O_3$·9/10H_2O) C, H, N.

Compound **6b** was prepared from **5** according to a similar procedure.

Method B. Preparation of 1-*N*-(3-*N*-(*tert*-Butoxycarbonyl)aminobenzyl)-3-(3-phenylureido)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (7). A solution of phenyl isocyanate (45 μL, 0.412 mmol) in DMF (0.5 mL) was added to a solution of compound **6a** (150 mg, 0.393 mmol) in DMF (3 mL) at 0 °C and was stirred at room temperature overnight. The reaction mixture was diluted with water and extracted with EtOAc. The organic extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (Et_2O/*n*-hexane = 3/2) to afford **7** (137 mg, 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. ($C_{29}H_{32}N_4O_4$·1/10H_2O) C, H, N.

Compounds **26**, **29** (from **6b**), and **44b**−**g** (from **42**) were prepared according to a similar procedure.

Method C. Preparation of 1-*N*-(3-(*N*-(3-Isopropylureido)-benzyl)-3-(3-(pyridin-4-yl)ureido)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (8). 3-((Imidazol-1-yl)carbonylamino)-1-*N*-(3-(*N*-(3-isopropylureido))benzyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one. To a solution of compound **6b** (5.02 g, 13.7 mmol) in CH_3CN (55 mL) was added carbonyldiimidazole (2.67 g 16.5 mmol) at 0 °C. After the mixture was stirred at room temperature for 1.5 h, it was poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was triturated with Et_2O to give 6.86 g (quantitative) of the title compound: ^{1}H NMR (CD_3OD) δ 1.15 (6H, d, J = 6.6 Hz), 2.42 (2H, m), 2.53−2.77 (2H, m), 3.85 (1H, m), 4.45 (1H, dd, J = 8.0 Hz, 11.5 Hz), 4.87 (1H, d, J = 14.7 Hz), 5.24 (1H, d, J = 14.7 Hz), 6.85 (1H, d, J = 7.5 Hz), 7.04 (1H, m), 7.13 (1H, t, J = 8.0 Hz), 7.19−7.42 (6H, m), 7.68 (1H, s), 8.30 (1H, s).

1-*N*-(3-(*N*-(3-Isopropylureido)benzyl)-3-(3-(pyridin-4-yl)ureido)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (8). To a suspension of 3-((imidazol-1-yl)carbonylamino)-1-*N*-(3-(*N*-(3-isopropylureido))benzyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (200 mg, 0.419 mmol) in CH_3CN (1 mL) was added 4-aminopyridine (160 mg, 0.838 mmol) at 0 °C, and the mixture stirred at room temperature for 1.5 h and was heated to reflux for 1.5 h. After cooling, the reaction mixture was poured into water. Extractive workup with EtOAc and PLC (EtOAc/MeOH = 5/1) afforded **8** (47 mg, 23%) as a powder: ^{1}H NMR (CD_3OD) δ 1.14 (6H, d, J = 6.6 Hz), 2.00 (1H, m), 2.35−2.74 (3H, m), 3.85 (1H, m), 4.35 (1H, dd, J = 7.8, 11.4 Hz), 4.81 (1H, d, J = 14.7 Hz), 5.29 (1H, d, J = 14.7 Hz), 6.84 (1H, d, J = 7.5 Hz), 7.12 (1H, t, J = 7.8 Hz), 7.16−7.42 (8H, m), 8.24 (2H, d, J = 6.6 Hz). Anal. ($C_{27}H_{30}N_6O_3$·3/10MeOH·1/10H_2O) C, H, N.

Compounds **9**−**25**, **28**, and **30**−**40** were prepared from **6b** according to a similar procedure.

Benzo[*b*]thiophene-5-isocyanate. To a suspention of benzo[*b*]thiophene-5-carboxylic acid (573 mg, 3.22 mmol) in toluene (5 mL) were added DMF (1 drop) and $SOCl_2$ (0.7 mL, 9.64 mmol). After the mixture was heated to reflux for 3 h, it was concentrated by distillation and the residue was dissolved in THF (6 mL). Sodium azide (230 mg, 3.54 mmol) was added, the mixture was stirred for 15 h and then filtered, and the filtrate was evaporated to dryness. The residue was dissolved in EtOAc and filtered and the filtrate was evaporated to dryness to afford benzothiophene-5-carbonyl azide (657 mg, quantitative) as crystals. Then a suspension of the carbonyl azide compound was dissolved in toluene (6 mL) and refluxed for 1 h. The filtrate was evaporated to dryness to give 563 mg (quantitative) of the title compound as crystals, which were used directly in the next step: benzothiophene-6-isocyanate was prepared in a similar manner.

Benzo[*b*]furan-6-amine. 6-Nitrobenzofuran (100 mg, 0.613 mmol) was hydrogenated in EtOH (5 mL) with 10% Pd−C (24 mg) under hydrogen atmosphere at room temperature for 15 min. After removal of the catalyst by filtration, the filtrate was evaporated to dryness. PLC (toluene/EtOAc = 7/1) afforded 50 mg (61%) of the title compound as an oil: ^{1}H NMR (DMSO-d_6) δ 1.07 (6H, d, J = 6.6 Hz), 6.61 (1H, dd, J = 1.2, 2.4 Hz), 6.68 (1H, dd, J = 2.4, 8.7 Hz), 6.87 (1H, d, J = 2.4 Hz), 8.29 (1H, d, J = 8.7 Hz), 7.53 (1H, d, J = 2.1 Hz).

Method D1. Preparation of 1-*N*-(3-(3-Isopropylureido)-benzyl)-3-(*N*-methyl-*N*-phenylguanidino)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (41a). 1-*N*-(3-(3-Isopropylureido)aminobenzyl)-3-(3-phenylthioureido)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one. To a solution of compound **6b** (300 mg, 0.819 mmol) in CH_3CN (1 mL) was added phenylthioisocynate (135 mg, 1.0 mmol) at 0 °C. After the mixture was stirred at room temperature for 1 h, the deposited crystals were collected by filtration to give 360 mg (85%) of

the title compound: mp 195−197 °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. ($C_{28}H_{31}N_5O_2S$) C, H, N, S.

1-*N*-(3-(3-Isopropylureido)benzyl)-3-(3-*S*-methylphenylisothioureido)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one. A suspension of the above thiourea compound (300 mg, 0.58 mmol) and MeI (0.3 mL, 4.8 mmol) in CH_3CN (1 mL) was heated to 40 °C with stirring for 1 h. After removal of the solvent, the residue was dissolved in water. The solution was basified to pH 10 with 20% aqueous Na_2CO_3 and was extracted with EtOAc. The extract was dried over K_2CO_3 and concentrated to afford 290 mg (94%) of the title 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-(3-Isopropylureido)benzyl)-3-(*N*-methyl-*N*′-phenylguanidino)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (41a). To 1-*N*-(3-(*N*′-(3-isopropylureido)benzyl)-3-(3-phenylthiomethylureido)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (230 mg, 0.433 mmol) was added 40% methylamine in MeOH solution (1 mL). 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 (CH_3CN/MeOH/AcOH = 3/1/0.2) to afford **41a** (140 mg, 38%) as a powder: ^{1}H NMR (CD_3OD) δ 1.14 (6H, d, *J* = 6.3 Hz), 1.98 (1H, m), 2.40−2.70 (3H, m), 2.73 (3H, s), 3.83 (1H, m), 4.30 (1H, dd, *J* = 7.2, 10.4 Hz), 4.88 (1H, d, *J* = 15.3 Hz), 5.14 (1H, d, *J* = 15.0 Hz), 6.83 (3H, m), 6.91 (1H, t, *J* = 7.5 Hz), 7.03 (1H, t, *J* = 7.5 Hz), 7.10−7.40 (8H, m). Anal. ($C_{28}H_{32}N_6O_2$·$0.3H_2O$) C, H, N.

Method D2. Preparation of 3-(*N*-(4-Hydroxyphenyl)-*N*′-methylguanidino)-1-*N*-(3-(3-isopropylureido)benzyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (41c). 1-*N*-(3-(3-Isopropylureido)benzyl)-3-(3-(4-(methoxymethyloxy)phenyl)thioureido)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one. Compound **6b** (1.22 g, 3.33 mmol) was dissolved in CH_3CN (12 mL) and cooled to −50 °C, and it was added thiocarbonyldiimidazole (1.40 g, 7.86 mmol). The mixture was stirred at the same temperature for 10 min and at room temperature for 10 min. 4-(Methoxymethyloxy)aniline (2.60 g, 17.0 mmol) was added. After 1 h the reaction mixture was 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 (toluene/EtOAc = 1/1) to afford 3.50 g (88%) of the title compound as a powder: ^{1}H NMR (CD_3OD) δ 1.14 (6H, d, *J* = 6.3 Hz), 1.95 (1H, m), 2.50−2.70 (3H, m), 3.43 (3H, s), 3.85 (1H, m), 4.83 (1H, d, 15.2 Hz), 5.00 (1H, dd, *J* = 6.0, 10.0 Hz), 5.17 (2H, s), 5.21 (1H, d, *J* = 15.2 Hz), 6.86 (1H, d, *J* = 7.0 Hz), 7.00−7.40 (11H, m).

3-(3-(4-Hydroxyphenyl)thioureido)-1-*N*-(3-(3-isopropylureido)benzyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one. A solution of the above 4-(methoxymethyloxy)phenyl compound (2.50 g, 4.45 mmol) in CH_2Cl_2 (10 mL) and trifluoroacetic acid (5 mL) was stirred at 0 °C for 1 h. After toluene (5 mL) was added, the mixture was concentrated to give 1.90 g (85%) of the title compound as a foam, which was used directly in the next step: ^{1}H NMR (CD_3OD) δ 1.13 (6H, *J* = 6.3 Hz), 1.95 (1H, m), 2.50−2.70 (3H, m), 3.85 (1H, m), 4.81 (1H, d, *J* = 14.7 Hz), 4.99 (1H, dd, 6.9, 10.8 Hz), 5.22 (1H, *J* = 14.7 Hz), 6.81 (2H, d, *J* = 8.7 Hz), 6.83 (1H, d, *J* = 7.0 Hz), 7.10 (1H, m), 7.11 (2H, d, *J* = 8.7 Hz), 7.20−7.40 (6H, m).

3-(3-(4-Hydroxyphenyl)-*S*-methylphenylisothioureido)-1-*N*-(3-(3-isopropylureido)benzyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one. A suspension of the above thiourea compound (1.80 g, 3.48 mmol) and MeI (3.0 mL, 46.5 mmol) in CH_3CN (30 mL) was stirred at room temperature for 3 h. After removal of the solvent, the residue was dissolved in water. The solution was basified to pH 10 with 20% aqueous Na_2CO_3 and was extracted with EtOAc. The extract was dried over K_2CO_3 and concentrated to afford 1.56 g (79%) of the title compound as a foam, which was used directly in the next step: ^{1}H NMR (CD_3OD) δ 1.14 (6H, *J* = 6.3 Hz), 2.1 (1H, m), 2.31 (3H, s), 2.50−2.70 (3H, m), 3.86 (1H, m), 4.97 (1H, d, *J* = 15.0 Hz), 5.11 (1H, d, *J* = 15.0 Hz), 6.50−6.70 (4H, m), 6.89 (1H, d, *J* = 7.2 Hz), 7.01 (1H, t, *J* = 7.8 Hz), 7.10−7.30 (6H, m).

3-(*N*-(4-Hydroxyphenyl)-*N*′-methylguanidino)-1-*N*-(3-(3-isopropylureido)benzyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (41c). The mixture of the above *S*-methylphenylisothioureido compound (200 mg, 0.376 mmol) and 20% methylamine in EtOH solution (2 mL) was heated to 70 °C with stirring in a sealed tube for 6 h. After removal of the solvent, the residue was purified by PLC (*n*-butanol/AcOH/H_2O = 5/1/1) to afford **41c** (52 mg, 27%) as a powder: ^{1}H NMR (CD_3OD) δ 1.13 (6H, dd, *J* = 1.8, 6.3 Hz), 2.05 (1H, m), 2.50−2.70 (3H, m), 2.82 (3H, s), 3.83 (1H, m), 4.30 (1H, dd, *J* = 7.2, 10.0 Hz), 4.85 (1H, d, *J* = 15.0 Hz), 5.20 (1H, d, *J* = 15.0 Hz), 6.63 (2H, d, *J* = 8.7 Hz), 6.75 (2H, d, *J* = 8.7 Hz), 6.80 (1H, t, *J* = 7.5 Hz), 7.07 (1H, t, *J* = 7.5 Hz), 7.20−7.40 (6H, m). Anal. ($C_{29}H_{34}N_6O_3$·$5/10H_2O$) C, H, N.

Compounds **41b**,**d**,**e** were prepared from **6b** according to a similar procedure.

1-*N*-(3-Aminobenzyl)-3-(3-phenylureido)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (42). A solution of compound **7** (1.61 g, 3.21 mmol) in CH_2Cl_2 (16 mL), anisole (5 mL), and trifluoroacetic acid (5 mL) was stirred at 0 °C for 10 min and at room temperature for an additional 3 h. After removal of the solvent, *n*-hexane (80 mL) was added, and the deposited precipitate was collected; 5% aqueous $NaHCO_3$ was added, and the mixture was extracted twice with ethyl acetate, washed with 5% aqueous $NaHCO_3$, H_2O, and brine, dried over Na_2SO_4, and concentrated to afford 1.36 g (quantitative) of the title compound as a foam: ^{1}H NMR (CD_3OD) δ 1.93−2.04 (1H, m), 2.36−2.71 (3H, m), 4.72−4.40 (1H, m), 4.79 (1H, d, *J* = 14.4 Hz), 5.17 (1H, d, *J* = 14.7 Hz), 6.53−6.65 (3H, m), 6.94−6.99 (2H, m), 7.19−7.34 (7H, m).

1-*N*-(3-*N*-(Methoxycarbonyl)aminobenzyl)-3-(3-phenylureido)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (43a). To a solution of compound **42** (158 mg, 0.375 mmol) in THF (4 mL) were added Et_3N (65 μL, 0.468 mmol) and methyl chloroformate (34 μL, 0.468 mmol) at 0 °C. The mixture was stirred at the same temperature for 1 h and at room temperature for an additional 1.4 h. The reaction mixture was 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 PLC (toluene/EtOAc = 1/1) to afford **43a** (85 mg, 49%) as a powder: ^{1}H NMR (CD_3OD) δ 2.00 (1H, m), 2.36−2.73 (3H, m), 3.70 (3H, s), 4.36 (1H, dd, *J* = 7.5, 11.4 Hz), 4.83 (1H, d, *J* = 15.0 Hz), 5.29 (1H, d, *J* = 15.0 Hz), 6.92 (1H, m), 7.12−7.37 (11H, m). Anal. ($C_{26}H_{26}N_4O_4$·$4/5H_2O$) C, H, N.

Compounds **43b**,**c** were prepared from **42** according to a similar procedure. Compounds **47** and **48** were prepared according to a similar procedure from compound **6a** and benzenesulfonyl chloride or phenyl chloroformate, respectively.

3-(3-Phenylureido)-1-*N*-(3-ureidobenzyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (44a). To a solution of compound **42** (200 mg, 0.475 mmol) in toluene (3 mL) and CH_3CN (0.5 mL) was added trichloroacetyl isocyanate (0.2 mL, 0.168 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h. The deposited solid was filtered, to which EtOAc (5 mL), MeOH (1 mL), and saturated $NaHCO_3$ aq. (3 mL) were added and stirred vigorously at room temperature overnight. After removal of MeOH, EtOAc was added and treated with silica gel. Then the silica gel was filtered off, and the filtrate was concentrated in vacuo. The residue was recrystallized from EtOAc to afford **44a** (145 mg, 63%): mp 210−215 °C; ^{1}H NMR (CD_3OD) δ 2.01 (1H, m), 2.4−2.6 (2H, m), 2.65 (1H, m), 4.36 (1H, dd, *J* = 7.4, 11.7 Hz), 4.83 (1H, d, *J* = 14.7 Hz), 5.28 (1H, d, *J* = 14.7 Hz), 6.87 (1H, d, *J* = 6.3 Hz), 6.96 (1H, t, *J* = 6.6

Hz), 7.14 (1H, t, J = 7.0 Hz), 7.10−7.40 (10H, m). Anal. ($C_{25}H_{25}N_5O_3$) C, H, N.

1-*N*-(3-*N*-(Morpholinocarbonyl)aminobenzyl)-3-(3-phenylureido)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (45). To a solution of compound **42** (200 mg, 0.499 mmol) in CH_2Cl_2 (2 mL) were added Et_3N (77 μL, 0.55 mmol) and 4-morpholinecarbonyl chloride (64 μL, 0.55 mmol) at −50 °C. The mixture was stirred at the same temperature for 1.3 h and at room temperature for 1.3 h; 5% aqueous $NaHCO_3$ was added, and the mixture was extracted twice with ethyl acetate, washed twice with H_2O and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by PLC (toluene/EtOAc/AcOH = 50/30/0.5) to afford **45** (85 mg, 33%) as a powder: ^{1}H NMR (CD_3OD) δ 2.00 (1H, m), 2.38−2.74 (3H, m), 3.44 (4H, m), 3.66 (4H, m), 4.36 (1H, dd, J = 7.5, 11.4 Hz), 4.90 (1H, d, J = 15.0 Hz), 5.21 (1H, d, J = 15.0 Hz), 6.90 (2H, m), 7.15−7.36 (11H, m). Anal. ($C_{29}H_{31}N_5O_4$·2/5Et_2O·5/10H_2O) C, H, N.

Preparation of 1-*N*-(3-(*N*′-(3-Isopropylureido))benzyl)-3-(phenylcarbamoyloxy)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (50). 3-(Phenylcarbamoyloxy)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one. To a solution of 3-(hydroxyoxy)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (42.8 mg, 0.241 mmol) in CH_3CN (1.0 mL) and THF (0.5 mL) were added phenyl isocyanate (27.5 μL, 0.253 mmol) and ($n$$Bu_3Sn)_2O$ (12 μL, 0.253 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 50 min and at room temperature for 30 min. After removal of the solvent, the residue was triturated with Et_2O to give 56.6 mg (80%) of the title compound as crystals, which were used directly in the next step: ^{1}H NMR (DMSO-d_6) δ 2.17−2.28 (1H, m), 2.45−2.59 (1H, m), 2.71−2.87 (2H, m), 4.83 (1H, dd, J = 7.8, 11.4 Hz), 6.95−7.44 (9H, m).

1-*N*-(3-(*N*′-(3-Isopropylureido))benzyl)-3-(phenylcarbamoyloxy)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (50). The above 3-phenylcarbamoyloxy compound (50 mg, 0.168 mmol) was added to a cooled mixture of 60% NaH (6.6 mg, 0.164 mmol) in DMF (1 mL) at 0 °C. The mixture was stirred for 30 min. Compound **4** (46 mg, 0.164 mmol) was added at 0 °C. After 30 min, it was partitioned between EtOAc and water. The aqueous phase was extracted with EtOAc, and combined organic extracts were washed four times with water and brine, dried over $MgSO_4$, and concentrated. PLC (toluene/EtOAc = 1/1) afforded **50** (72 mg, 89%) as a powder: ^{1}H NMR ($CDCl_3$) δ 1.12 (6H, d, J = 6.6 Hz), 2.20−2.76 (4H, m), 3.94 (1H, m), 4.61 (1H, d, J = 7.2 Hz), 4.91 (1H, d, J = 15.0 Hz), 5.09 (1H, d, J = 15.0 Hz), 5.09 (1H, dd, J = 7.8, 10.8 Hz), 6.72 (1H, s), 7.00−7.40 (12H, m), 7.61 (1H, d, J = 8.7 Hz). Anal. ($C_{28}H_{30}N_4O_4$·9/10H_2O) C, H, N.

Preparation of 3-Cyano-1-*N*-(3-(*N*′-(3-isopropylureido))benzyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (51). 3-Chloro-1-*N*-(3-(*N*′-(3-isopropylureido))benzyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one was prepared according to method A using 3-chloro-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one in 97% yield: ^{1}H NMR ($CDCl_3$) δ 1.15 (6H, d, J = 6.3 Hz), 2.35−2.63 (4H, m), 3.97 (1H, m), 4.44−4.50 (1H, m), 4.94 (1H, d, J = 14.7 Hz), 5.09 (1H, d, J = 14.7 Hz), 6.77 (2H, d, J = 6.3 Hz), 7.11−7.31 (6H, m), 7.42−7.45 (1H, m).

3-Cyano-1-*N*-(3-(*N*′-(3-isopropylureido))benzyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (51). A mixture of the above 3-chloro compound (5.0 g, 13.0 mmol), KCN (1.953 g, 34.9 mmol), and $n$$Bu_4NBr$ (388 mg, 3.49 mmol) in DMSO (20 mL) was heated to 115 °C with stirring for 9 h and stirred at room temperature overnight. The reaction mixture was partitioned between EtOAc and water. The aqueous phase was extracted with EtOAc, and combined organic extracts were washed four times with water and brine, dried over $MgSO_4$, and concentrated to give a foam. Trituration with EtOAc gave **51** (2.99 g, 59%) as crystals: mp 216−217 °C; ^{1}H NMR (DMSO-d_6) δ 1.07 (6H, d, J = 6.3 Hz), 2.39−2.61 (4H, m), 3.72 (1H, m), 3.84 (1H, t, J = 9.6 Hz), 4.73 (1H, d, J = 14.7 Hz), 5.21 (1H, d, J = 14.7 Hz), 5.91 (1H, d, J = 7.5 Hz), 6.69 (1H, d, J = 7.8 Hz), 7.07−7.44 (7H, m), 8.27 (1H, s); HR-FABMS m/z (M + H)$^+$ 377.1975 (calcd for $C_{22}H_{25}N_4O_2$ m/z 377.1976).

Preparation of 1-*N*-(3-(*N*′-(3-Isopropylureido))benzyl)-3-((3-phenylureido)methyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (52). 3-(Aminomethyl)-1-*N*-(3-(*N*′-(3-isopropylureido))benzyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one. A solution of compound **51** (500 mg, 1.33 mmol) in EtOH (10 mL) and 12 N HCl (0.33 mL) was hydrogenated over 10% Pd−C (300 mg) at 4.0 kg/cm^2 overnight. After removal of the catalyst by filtration, the filtrate was evaporated to dryness. The residue was partitioned between EtOAc and 1 N HCl. The aqueous phase was basified with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic phase was washed with water and brine, dried over $MgSO_4$, and concentrated to give 340 mg (67%) of the title compound, which was used directly in the next step: ^{1}H NMR (DMSO-d_6) δ 1.07 (6H, d, J = 6.6 Hz), 1.88−1.91 (1H, m), 2.03−2.14 (1H, m), 2.63−2.69 (1H, m), 2.99−3.06 (1H, m), 4.75 (1H, d, J = 15.3 Hz), 5.22 (1H, d, J = 14.7 Hz), 6.04 (1H, d, J = 7.8 Hz), 6.70 (1H, d, J = 7.5 Hz), 7.04−7.39 (7H, m), 8.43 (1H, s); HR-FABMS m/z (M + H)$^+$ 381.2291 (calcd for $C_{22}H_{29}N_4O_2$ m/z 381.2289).

1-*N*-(3-(*N*′-(3-Isopropylureido))benzyl)-3-((3-phenylureido)methyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (52) was prepared according to method B using the 3-aminomethyl compound in 26% yield: mp 223−226 °C; ^{1}H NMR (DMSO-d_6) δ 1.07 (6H, d, J = 6.6 Hz), 1.80−2.10 (2H, m), 2.39−2.55 (3H, m), 3.25 (2H, dd, J = 6.0, 6.0 Hz), 3.72 (1H, m), 4.70 (1H, d, J = 15.0 Hz), 5.31 (1H, d, J = 15.0 Hz), 5.91 (1H, d, J = 7.8 Hz), 6.30 (1H, t, J = 6.0 Hz), 6.69 (1H, d, J = 7.5 Hz), 6.85 (1H, t, J = 7.5 Hz), 7.00−7.40 (11H, m), 8.26 (1H, s), 8.52 (1H, s). Anal. ($C_{29}H_{33}N_5O_3$) C, H, N.

Preparation of 3-Carboxy-1-*N*-(3-(*N*′-(3-isopropylureido))benzyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (53). 1-*N*-(3-(*N*′-(3-Isopropylureido))benzyl)-3-(methoxycarbonyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one. A suspension of compound **51** (300 mg, 0.797 mmol) in 10% HCl in MeOH solution (4.5 mL) and a small amount of THF were heated in a sealed tube at 70 °C for 3 h and at 50 °C for 14 h. After concentration, 10% HCl in MeOH solution (7 mL) was added to the residue; the solution was heated in a sealed tube at 80 °C for 32 h. It was poured into water and extracted with EtOAc. The organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated. PLC (toluene/EtOAc = 1/1) afforded 150 mg (46%) of the title compound as a foam, which was used directly in the next step: ^{1}H NMR (DMSO-d_6) δ 1.07 (6H, d, J = 6.6 Hz), 2.15 (1H, m), 2.44−2.58 (3H, m), 3.30 (1H, m), 3.58 (3H, m), 3.72 (1H, m), 4.66 (1H, brs), 5.27 (1H, brs), 5.71 (1H, d, J = 7.5 Hz), 6.67 (1H, d, J = 7.5 Hz), 7.06 (1H, t, J = 7.8 Hz), 7.10−7.50 (6H, m), 8.27 (1H, m); HR-FABMS m/z (M + H)$^+$ 410.2081 (calcd for $C_{23}H_{28}N_3O_4$ m/z 410.2079).

3-Carboxy-1-*N*-(3-(*N*′-(3-isopropylureido))benzyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (53). To the above 3-methyl ester compound (125 mg, 0.305 mmol) was added 4 N aqueous NaOH (0.14 mL) at 0 °C. The mixture was stirred at room temperature for 3 h 20 min. After removal of the solvent, 1 N HCl was added and the mixture extracted with EtOAc. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated to afforded 125 mg (quantitative) of the title compound as a foam, which was used directly in the next step: ^{1}H NMR (DMSO-d_6) δ 1.07 (6H, d, J = 6.6 Hz), 2.15 (1H, m), 2.44−2.51 (1H, m), 3.72 (1H, m), 4.71 (2H, m), 5.23 (2H, m), 5.90 (1H, d, J = 7.2 Hz), 6.69 (1H, d, J = 7.8 Hz), 7.42−7.83 (7H, m), 8.25 (1H, s), 12.37 (1H, s).

Preparation of 1-*N*-(3-(*N*′-(3-Isopropylureido))benzyl)-3-(phenylcarbamoyloxymethyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (54). 3-(Hydroxymethyl)-1-*N*-(3-(*N*′-(3-isopropylureido))benzyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one. Compound **53** (753 mg, 0.19 mmol) was esterified by diazomethane. To a solution of the resulting 3-methoxycarbonyl compound in THF (2 mL) was added $LiBH_4$ (42 mg, 1.93 mmol) at 0 °C, and the mixture was stirred at room temperature for 1 h 15 min. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The organic extracts were washed with H_2O and brine,

dried over $MgSO_4$, and concentrated in vacuo. Trituration with EtOAc gave 247 mg (34%) of the title compound as crystals: mp 87−91 °C; ^{1}H NMR ($CDCl_3$ + CD_3OD) δ 1.15 (6H, d, *J* = 6.3 Hz), 1.99−2.11 (2H, m), 2.51−2.68 (3H, m), 3.63 (1H, dd, *J* = 3.9, 12.6 Hz), 3.79−3.95 (2H, m), 4.92 (1H, d, *J* = 15.0 Hz), 5.02 (1H, d, *J* = 15.3 Hz), 6.77 (1H, d, *J* = 7.5 Hz), 7.05 (1H, m), 7.14−7.26 (5H, m), 7.49 (1H, dd, *J* = 2.1, 8.4 Hz). Anal. ($C_{22}H_{27}N_3O_3$·1/5H_2O) C, H, N.

1-*N*-(3-(*N'*-(3-Isopropylureido))benzyl)-3-(phenylcarbamoyloxymethyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (54) was prepared in a similar to that described in the preparation of compound **52** using the 3-hydroxymethyl compound: 73% yield; ^{1}H NMR ($CDCl_3$) δ 1.11 (6H, d, *J* = 6.6 Hz), 1.94 (4H, m), 2.12 (1H, m), 2.50−2.72 (2H, m), 2.84 (1H, m), 3.92 (1H, m), 4.25 (1H, m), 4.50 (1H, m), 4.66 (1H, d, *J* = 8.1 Hz), 4.81 (1H, d, *J* = 15.0 Hz), 5.16 (1H, d, *J* = 15.0 Hz), 6.63 (1H, s), 6.85 (1H, d, *J* = 7.2 Hz), 6.72 (1H, s), 7.00−7.36 (13H, m). Anal. ($C_{29}H_{31}N_4O_4$·3/10H_2O) C, H, N.

3-(Anilinocarbonyl)-1-*N*-(3-(*N'*-(3-isopropylureido))-benzyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (55). To a solution of compound **53** (110 mg, 0.278 mmol), HOBT (3.8 mg, 0.028 mmol), and aniline (25 mL, 0.278 mmol) in THF (1 mL) was added 1-(3-(dimethylamino)propyl)-3-ethoxycarbonyldiimide hydrochloride (43 mg, 0.278 mmol) at 0 °C, and the mixture was stirred at room temperature for 3 h. The reaction mixture was partitioned between EtOAc and water. The aqueous phase was extracted with EtOAc, combined organic extracts were washed with H_2O and brine, dried over $MgSO_4$, and concentrated, and the deposited solid was collected. Trituration with Et_2O gave **55** (61 mg, 47%) as a powder: ^{1}H NMR (DMSO-*d*$_6$) δ 1.07 (6H, d, *J* = 6.6 Hz), 2.05 (4H, m), 2.50−2.70 (3H, m), 3.40 (1H, m), 3.72 (1H, m), 4.70 (1H, d, *J* = 15.0 Hz), 5.30 (1H, d, *J* = 15.0 Hz), 5.90 (1H, d, *J* = 7.5 Hz), 6.73 (1H, d, *J* = 7.5 Hz), 7.00−7.40 (9H, m), 7.49 (1H, d, *J* = 7.8 Hz), 7.55 (2H, d, *J* = 7.5 Hz), 8.26 (1H, s), 9.84 (1H, s). Anal. ($C_{28}H_{30}N_4O_3$·3/10H_2O) C, H, N.

Preparation of Methyl 3-(Isopropylaminocarbonylmethyl)benzoate (57). (i) A suspension of dimethyl isophthalate (7.02 g, 36.2 mmol) in 1 M NaOH in MeOH solution was stirred overnight. The mixture was neutralized with HCl and evaporated to dryness. The residue was partitioned between toluene and saturated aqueous $NaHCO_3$. The aqueous phase was acidified with concentrated aqueous HCl and extracted with EtOAc. The organic extract was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated. Trituration with EtOAc gave the monocarboxylic acid (4.0 g, 61%) as crystals: ^{1}H NMR (DMSO-*d*$_6$) δ 3.90 (3H, s), 7.68 (1H, t, *J* = 7.5 Hz), 8.18−8.22 (2H, m), 8.49 (1H, s), 13.31 (1H, brs).

(ii) To thionyl chloride (3.40 mL, 46.9 mmol) in toluene (20 mL) was added the above monocarboxylic acid compound (4.02 g, 23.3 mmol) and DMF (3 drops). The mixture was heated to 92 °C with stirring for 50 min and then concentrated in vacuo to give an oil. A solution of diazomethane in Et_2O was added dropwise to the oil at 0 °C and evaporated to dryness to give the diazo compound (4.77 g, quantitative): ^{1}H NMR ($CDCl_3$) δ 3.95 (3H, s), 5.99 (1H, s), 7.55 (1H, t, *J* = 7.5 Hz), 8.02 (1H, dt, *J* = 1.5, 7.8 Hz), 8.21 (1H, dt, *J* = 1.5, 7.5 Hz), 7.36 (1H, t, *J* = 7.8 Hz).

(iii) A solution of the above diazo compound in 1,4-dioxane (64 mL) was added to a suspension of Ag_2O (680 mg, 2.94 mmol) in H_2O and heated to 55 °C. After 15 min, Ag_2O (680 mg, 2.94 mmol) was added, continued to stir at 55 °C for 10 min, and concentrated. Workup was done the same as in (i) to give the monocarboxylic acid 1.137 g (60%) as an oil: ^{1}H NMR (DMSO-*d*$_6$) δ 3.48 (2H, s), 3.84 (3H, s), 7.39 (1H, t, *J* = 7.5 Hz), 7.50 (1H, d, *J* = 7.8 Hz), 8.21 (1H, d, *J* = 7.8 Hz), 7.76 (1H, t, *J* = 7.5 Hz), 7.86 (1H, s).

(iv) To the above carboxylic acid compound (500 mg, 2.58 mmol) in toluene (2 mL) were added oxalyl chloride (0.675 mL, 7.73 mmol) in toluene (2 mL) and DMF (3 drops). The reaction mixture was heated to 50 °C and stirred for 15 min. After concentrated, the resulting oil was dissolved in toluene (1 mL). Isopropylamide (0.88 mL, 10.3 mmol) was added at 0 °C and stirred for 20 min. The mixture was filtered, and the residue was partitioned between EtOAc and 1 N HCl. The aqueous phase was extracted with EtOAc. The organic extract was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated to give **57** (302 mg, 50%) as a powder: ^{1}H NMR ($CDCl_3$) δ 1.05 (6H, d, *J* = 6.6 Hz), 3.44 (2H, s), 3.80 (1H, s), 3.85 (3H, s), 7.42−7.54 (2H, m), 7.80−7.88 (2H, m), 7.90 (1H, d, *J* = 7.2 Hz). Anal. ($C_{13}H_{17}NO_3$) C, H, N.

3-(Isopropylaminocarbonylmethyl)benzyl Bromide (58). To a solution of compound **57** (457 mg, 1.94 mmol) in THF (9.5 mL) was added 0.878 M $LiBH_4$ in THF solution (3.93 mL) at −65 °C. The mixture was warmed to 0 °C with stirring for 30 min. It was cooled to −55 °C, then H_2O was added, and it was warmed to room temperature. After filtration, the filtrate was concentrated in vacuo to give the alcohol compound (400 mg). To the alcohol compound (100 mg, 0.482 mmol) in THF (1 mL) were added PPh_3 (140 g, 0.53 mmol) and NBS (82 mg, 0.458 mmol). The mixture was stirred for 30 min, and *n*-hexane was added. The resulting precipitate was filtered off, and the filtrate was concentrated. The residue was purified by PLC (EtOAc/toluene = 1/1) to afford **58** (87 mg, 67%) as crystals: mp 94−97 °C; ^{1}H NMR ($CDCl_3$) δ 1.09 (6H, d, *J* = 6.6 Hz), 3.52 (2H, s), 4.07 (1H, m), 4.49 (2H, s), 5.18 (1H, brs), 7.18−7.34 (4H, m). Anal. ($C_{12}H_{16}NOBr$) C, H, N, Br.

1-*N*-(3-Isopropylaminocarbonylmethyl)-3-(3-phenylureido)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (59) was prepared according to the same procedure from **5** to **7** using compound **58** in 77% yield: mp 178−179 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.82 (3H, d, *J* = 6.6 Hz), 0.99 (3H, d, *J* = 6.6 Hz), 2.00 (1H, m), 2.45−2.90 (3H, m), 3.29 (1H, d, *J* = 14.0 Hz), 3.37 (1H, d, *J* = 14.0 Hz), 3.93 (1H, m), 4.60 (1H, m), 4.74 (1H, d, *J* = 15.6 Hz), 5.46 (1H, d, *J* = 15.6 Hz), 6.33 (1H, d, *J* = 7.8 Hz), 6.47 (1H, d, *J* = 8.2 Hz), 6.80−7.40 (14H, m). Anal. ($C_{29}H_{32}N_4O_3$) C, H, N.

Preparation of 5-*N*-(3-(3-Isopropylureido)benzyl)-3-(3-phenylureido)-2,3-dihydro-5*H*-1,5-benzoxazepin-4-one (63). 3-(*tert*-Butoxycarbonylamino)-5-*N*-(3-(3-isopropylureido)benzyl)-2,3-dihydro-5*H*-1,5-benzoxazepin-4-one was prepared according to method A using 3-(*tert*-butoxycarbonylamino)-2,3-dihydro-5*H*-1,5-benzoxazepin-4-one in 70% yield: mp 197−205 °C; ^{1}H NMR (CD_3OD) δ 1.15 (6H, d, *J* = 6.6 Hz), 1.41 (9H, s), 3.85 (1H, m), 4.28−4.45 (2H, m), 4.59−4.66 (1H, m), 4.63 (1H, dd, *J* = 7.8, 11.4 Hz), 4.90 (1H, d, *J* = 15.6 Hz), 5.26 (1H, d, *J* = 15.9 Hz), 6.85 (1H, d, *J* = 7.2 Hz), 6.83−7.40 (8H, m).

3-Amino-5-*N*-(3-(3-isopropylureido)benzyl)-2,3-dihydro-5*H*-1,5-benzoxazepin-4-one. To the 3-BOC compound (240 mg, 0.512 mmol) was added 4 N HCl in EtOAc solution at 0 °C. The mixture was stirred at room temperature for 0.5 h. The reaction mixture was evaporated to dryness, and the residue was washed with Et_2O; 5% aqueous $NaHCO_3$ was added, and the mixture was extracted twice with ethyl acetate, washed twice with H_2O and brine, dried over $MgSO_4$, and concentrated to afford 150 mg (80%) of the title compound as a powder, which was used directly in the next step: ^{1}H NMR (CD_3OD) δ 1.15 (6H, d, *J* = 6.3 Hz), 3.81−3.89 (2H, m), 4.15−4.22 (1H, m), 4.39−4.45 (1H, m), 4.96 (1H, d, *J* = 15.9 Hz), 5.20 (1H, d, *J* = 15.0 Hz), 6.87 (1H, d, *J* = 7.5 Hz), 7.11−7.37 (7H, m).

5-*N*-(3-(3-Isopropylureido)benzyl)-3-(3-phenylureido)-2,3-dihydro-5*H*-1,5-benzoxazepin-4-one (63) was prepared according to method B in 81% yield: mp 237−239.5 °C; ^{1}H NMR (CD_3OD + DMSO-*d*$_6$) δ 1.13 (6H, d, *J* = 6.6 Hz), 3.82 (1H, m), 4.30 (1H, m), 4.55 (1H, m), 4.84 (1H, dd, *J* = 7.8, 11.4 Hz), 4.93 (1H, d, *J* = 15.9 Hz), 5.29 (1H, d, *J* = 15.9 Hz), 6.85 (1H, d, *J* = 7.8 Hz), 6.97 (1H, t, *J* = 7.2 Hz), 7.10−7.50 (11H, m). Anal. ($C_{28}H_{32}N_6O_3$·3/10H_2O) C, H, N.

1-*N*-(3-(*N'*-(3-Isopropylureido))benzyl)-3-(3-phenylureido)-3,4,5,6-tetrahydro-1*H*-1-benzazocin-2-one (66) was prepared according to the same procedure from **5** to **7** using compound **65** in 44% yield: mp 241−244 °C; ^{1}H NMR (DMSO-*d*$_6$) δ 1.06 (6H, d, *J* = 6.6 Hz), 1.30 (1H, m), 1.75 (2H, brs.), 2.00 (2H, m), 2.50 (2H, m), 3.70 (1H, m), 3.80 (1H, m), 4.55 (1H, d, *J* = 14.4 Hz), 5.19 (1H, d, *J* = 14.4 Hz), 5.91 (1H, d, *J*

= 7.5 Hz), 6.58 (2H, d, J = 8.1 Hz), 6.66 (1H, d, J = 7.2 Hz), 6.87 (1H, t, J = 7.2 Hz), 7.05–7.35 (11H, m), 8.24 (1H, s), 8.71 (1H, s). Anal. ($C_{29}H_{33}N_5O_3$·4/5H_2O) C, H, N.

4-(Hydroxymethyl)-2-(isopropylureido)thiazole (68) was prepared in a similar manner to that described in the preparation of compound **5** in 44% yield: mp 163–165 °C; ^{1}H NMR (DMSO-d_6) δ 1.11 (6H, d, J = 6.3 Hz), 3.37 (1H, m), 4.37 (2H, d, J = 6.0 Hz), 5.11 (1H, t, J = 6.0 Hz), 6.41 (1H, d, J = 7.5 Hz), 6.70 (1H, s). Anal. ($C_8H_{13}N_3O_2S$) C, H, N, S.

4-(Bromomethyl)-2-(isopropylureido)thiazole (69) was prepared in a similar manner to that described in the preparation of compound **58** using **68** in 25% yield: mp 94–97 °C; ^{1}H NMR ($CDCl_3$) δ 1.26 (6H, d, J = 6.6 Hz), 4.03 (1H, m), 4.45 (2H, s), 6.78 (1H, s). Anal. ($C_{12}H_{16}NOBr$) C, H, N.

Preparation of 3-((3-(2,4-Difluorophenyl)ureido)methyl)-1-*N*-(2-(isopropylureido)thiazol-4-ylmethyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (71). 3-((3-(2,4-Difluorophenyl)ureido)methyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one was prepared according to method B using 3-amino-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one, **70**,[24] and 2,4-difluorophenyl isocyanate: 91% yield; mp 193–195 °C; ^{1}H NMR (DMSO-d_6) δ 1.87–1.97 (1H, m), 2.37–2.48 (1H, m), 2.66–2.82 (2H, m), 4.14 (1H, dd, J = 7.5, 9.0 Hz), 6.91–7.33 (6H, m), 7.91–7.99 (1H, m).

3-((3-(2,4-Difluorophenyl)ureido)methyl)-1-*N*-(2-(isopropylureido)thiazol-4-ylmethyl)-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (71). To a solution of the amido compound (100 mg, 0.302 mmol) in THF (1 mL) was added 1.58 M *n*BuLi in hexane solution (0.21 mL) at −55 °C, and then compound **4** (101 mg, 0.362 mmol) in THF (2 mL) was added during 3 min. The reaction temperature was raised to room temperature with stirring during 1 h 20 min and continued to stir for 1 h 45 min. The reaction mixture was partitioned between EtOAc and water. The aqueous phase was extracted with EtOAc, and combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated. PLC (toluene/EtOAc = 2/1) afforded **71** (29 mg, 18%) as crystals: mp > 270 °C; ^{1}H NMR (DMSO-d_6) δ 1.08 (6H, dd, J = 1.2, 6.6 Hz), 1.18 (1H, m), 2.25–2.60 (2H, m), 2.82 (1H, m), 3.74 (1H, m), 4.17 (1H, m), 4.77 (1H, d, J = 15.0 Hz), 5.13 (1H, d, J = 15.0 Hz), 6.37 (1H, d, J = 6.9 Hz), 6.69 (1H, s), 6.94 (1H, m), 7.04 (1H, d, J = 7.5 Hz), 7.16–7.35 (5H, m), 7.47 (1H, d, J = 8.1 Hz), 7.95 (1H, m), 8.56 (1H, s), 10.18 (1H, s). Anal. ($C_{25}H_{26}N_6O_3SF_2$·1/5H_2O) C, H, N, S, F.

NPY Receptor Binding Assay. NPY Y1 and Y2 receptor binding assays were conducted as described previously[37,38] 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 nonspecific binding of the former was lower than that of 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). 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. The incubation was stopped by removal of 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.[39] NPY Y4 receptor binding was carried out with rat liver membranes according to the method of Nguyen et al.[40]

Measurement of Cytosolic Free Ca^{2+} Concentration.[37] SK-N-MC cells were dispersed with 0.025% trypsin/1 mM EDTA. Cells were washed once with 20 nM HEPES-buffered Hank's solution (pH 7.4) and resuspended with the same buffer to a concentration of 1×10^6 cells/mL. The cell suspension was incubated with 2 mM fura-2-AM at 37 °C for 30 min. The fura-2-loaded cells thus obtained were resuspended in 0.3 mL of 20 mM HEPES-buffered Hank's solution (pH 7.4) at a concentration of 0.5×10^6 cells/mL in a cuvette (50-mm × 7-mm diameter) and continuously stirred. Antagonists were added 1 min before the addition of NPY or endothelin-1. Fluorescence measurements were done with a spectrofluorometer (CAF-100, Japan Spectroscopy Inc., Tokyo, Japan) as described previously.[7]

Histamine Experiments.[41] Histamine release was determined after 48-h short-term culture by incubating isolated ECL cells in a six-well plate containing 1 mL of HBSS. Cells (2×10^5/well plate) were stimulated by 5×10^{-9} M gastrin-17 with or without 1×10^{-8} M PYY at 37 °C for 60 min. **21** (2×10^{-6} M) was added 30 min before the stimulation. Dimethyl sulfoxide was used as a vehicle for **21** at a final concentration of less than 0.5%, which did not alter histamine release. Histamine content was determined by the HPLC method.

Supporting Information Available: Characteristic data for part of the synthetic intermediates and final products. This material is available free of charge via the Internet at http://pubs.acs.org.

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