# Synthesis and Evaluation of a Series of Novel 2-[(4-Chlorophenoxy)methyl]-benzimidazoles as Selective Neuropeptide Y Y1 Receptor Antagonists

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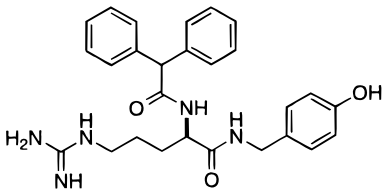
A series of novel benzimidazoles (BI) derived from the indole **2** was synthesized and evaluated as selective neuropeptide Y (NPY) Y1 receptor antagonists with the aim of developing antiobesity drugs. In our SAR approach, the (4-chlorophenoxy)methyl group at C-2 was kept constant and a series of BIs substituted with various piperidinylalkyl groups at N-1 was synthesized to identify the optimal spacing and orientation of the piperidine ring nitrogen relative to the benzimidazole. The 3-(3-piperidinyl)propyl in **33** was found to maximize affinity for the Y1 receptor. Because of the critical importance of $Arg^{33}$ and $Arg^{35}$ of NPY binding to the Y1 receptor, the incorporation of an additional aminoalkyl functionality to the structure of **33** was explored. Methyl substitution was used to probe where substitution on the aromatic ring was best tolerated. In this fashion, the C-4 was chosen for the substitution of the second aminoalkyl functionality. Synthesis of such compounds with a phenoxy tether using the 4-hydroxybenzimidazole **11** was pursued because of their relative ease of synthesis. Functionalization of the hydroxy group of **45** with a series of piperidinylalkyl groups provided the dibasic benzimidazoles **55**−**62**. Among them, BI **56** demonstrated a $K_i$ of 0.0017 $\mu$M, which was 400-fold more potent than **33**. To evaluate if there was a stereoselective effect on affinity for these BIs, the four constituent stereoisomers (**69**−**72**) of the BI **60** were prepared using the *S*- and *R*-isomers of bromide **17**. Antagonist activity of these BIs was confirmed by measuring the ability of selected compounds to reverse NPY-induced forskolin-stimulated cyclic AMP. The high selectivity of several BI antagonists for the Y1 versus Y2, Y4, and Y5 receptors was also shown.

## Introduction

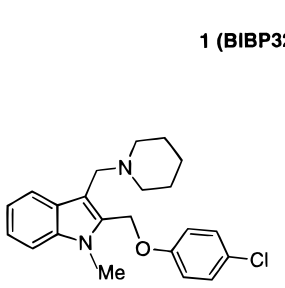
Neuropeptide Y (NPY) is a 36-amino-acid peptide that was first isolated in 1982 from porcine brain.[1] NPY belongs to the pancreatic polypeptide (PP) family of structurally related peptides and is known to be the most abundant peptide in the central nervous system of all the mammalian species studied to date.[2] It is also widely distributed throughout the peripheral nervous system.[3] NPY is believed to be involved in a broad spectrum of brain functions, including food intake,[4−6] blood pressure regulation,[7,8] hormone secretion,[9] sexual behavior,[10] and circadian rhythm.[7] Chronic injection of NPY in rats produces severe overeating, particularly of carbohydrate and fat, that leads to the development of obesity.[6]

Neuropeptide Y exerts its effect by interacting with its receptor subtypes,[11] which are distributed in both peripheral and central tissues.[12] At least six of these receptor subtypes have been identified to date (Y1−Y6). Until the recent discovery of the Y5[13,14] subtype, Y1 was believed to be the best candidate for the feeding receptor[4,15] and, therefore, a target for developing antagonists as a treatment for obesity.[16−19]

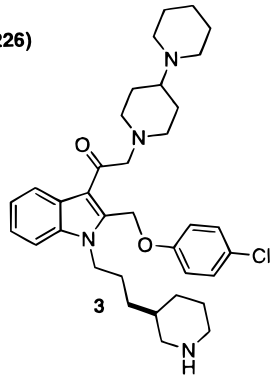
The discovery of other Y1 antagonists having peptide and nonpeptide structures has been previously reported.[20−24] Compound **1** (BIBP3226) is the best characterized Y1 antagonist and has proven to be a useful tool for studying NPY receptors.[25] However, because of its limited potency and activity following systemic administration, there is still a need to develop other selective antagonist ligands for the Y1 receptor for use as pharmacological probes and possibly as therapeutic agents.




**1 (BIBP3226)**




**2**




**3**

The genesis of this study was the discovery of indole

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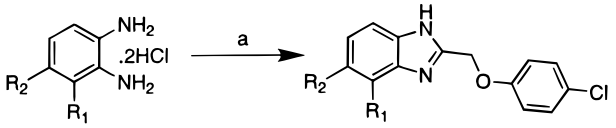
**Scheme 1**[a]



| | $R_1$ | $R_2$ | |
|---|---|---|---|
| **4** | H | H | **8** |
| **5** | $CH_3$ | H | **9** |
| **6** | H | $CH_3$ | **10** |
| **7** | OH | H | **11** |

[a] Key: (a) (4-chlorophenoxy)acetonitrile, MeONa, MeOH, rt.

**2** as a Y1 receptor ligand. Key features of this molecule for binding to the Y1 receptor included an aminoalkyl substituent at N-1 and a (4-chlorophenoxy)methyl substituent at C-2. Subsequent optimization of **2**, performed in conjunction with the research reported in this account, afforded **3** with significantly higher Y1 receptor affinity.[26]

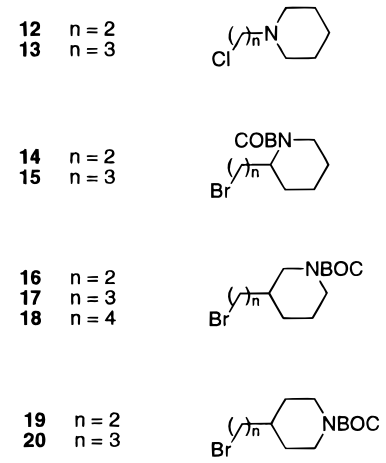
To further expand the scope of the structure activity studies related to **2**, we chose to examine if other nuclei could substitute for the indole nucleus in **2**. We postulated the benzimidazole (BI) as such a replacement and recognized that a BI, while not isoelectronic to an indole, is isosteric. Furthermore, BIs are readily prepared, easily functionalized, and are often more stable than indoles. In this paper, we describe the synthesis of novel BIs and their characterization as Y1 antagonists. The structure−activity relationships of various piperidinylalkyl groups at N-1 and the effect of a second piperidinylalkyl group on the aromatic ring with a C-2, (4-chlorophenoxy)methyl substituent were determined.

## Chemistry

Our basic synthetic strategy involved preparing the BI nuclei, followed by alkylation with the appropriate piperidinylalkyl halide. To further define structural requirements for activity at N-1, we prepared a variety of BIs substituted with various piperidinylalkyl groups, where the spacing and orientation of the piperidine ring nitrogen relative to the benzimidazole were varied. The parent BI **8** was prepared by condensation of phenylenediamine (**4**) with (4-chlorophenoxy)acetonitrile, as shown in Scheme 1. The requisite piperidinylalkyl halides were either commercially available (**12** and **13**; Chart 1) or were prepared according to published procedures (**14**−**20**; Chart 1).[27,28] Deprotonation of **8** (NaH, DMF, 80 °C) followed by alkylation with **12** and **13** afforded the desired BIs **21** and **22** (Scheme 2). Alternatively, alkylation with the *N*-BOC-protected bromides **14**−**20** afforded **23**−**29**, which gave BIs **30**−**36** after deprotection with trifluoroacetic acid in dichloromethane (Scheme 2).

Our ultimate goal beyond N-1 substitution was to incorporate a second aminoalkyl functionality in these BIs to probe for other amine recognition domains on the receptor. To identify the best place on the aromatic ring to incorporate this group, we prepared BIs with a methyl group at each of the four substitutable positions on the aromatic ring. To this end, we prepared BIs **9** and **10** from the corresponding methyl-substituted phenylenediamines **5** and **6**, respectively, as shown in Scheme 1. On the basis of our SAR findings (vide infra), for this aspect of the study we chose to use a (3-piperidinyl)propyl group N-1-substituted BI. Alkylation of **9** with **17** afforded a separable 3:1 mixture of the 4- and 7-methyl compounds **37** and **38**, respectively (favoring the 4-methyl compound **37**). Each gave the desired BIs **40** and **41**, respectively, after deprotection (Scheme 3). The structures of **40** and **41** were confirmed by NOE spectroscopy. In $MeOD_4$, **40** showed an NOE between the methyl at C-4 (singlet at $\delta$ 2.65) and the proton at C-5 (doublet at $\delta$ 7.36) and an NOE between the protons on the methylene adjacent to N-1 (triplet at $\delta$ 4.61) and the proton at C-7 (doublet at $\delta$ 7.61). Alkylation of **10** with **17** afforded an inseparable mixture of the 5- and 6-methyl compounds **39**, which upon deprotection gave BI **42**, also as an inseparable mixture of regioisomers (Scheme 3).

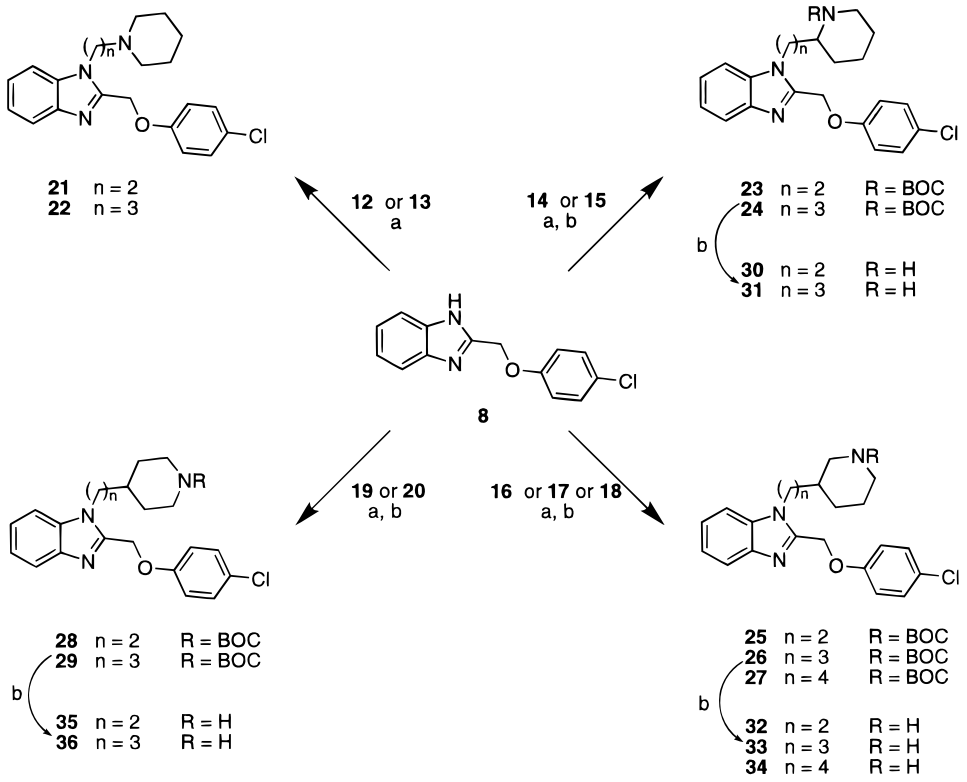
**Chart 1**



Substitution on the aromatic ring with a second piperidinylalkyl group at C-4 was achieved by conversion of **7** to the 4-hydroxy BI **11** (Scheme 1), which was selectively *O*-benzylated under Mitsunobu conditions ($Ph_3P$, DEAD, THF, 0 °C to room temperature) to give **43** (Scheme 4). This selective protection strategy offered us the opportunity to incorporate different aminoalkyl groups at N-1 and C-4. Alkylation of **43** with **17** gave **44**, which after hydrogenolysis of the benzyl group yielded **45** (Scheme 4). Deprotection of **45** as before gave **46**. As used for the alkylation at N-1, **45** was deprotonated with sodium hydride in dimethylformamide and then reacted with **12**−**17**, **19**, and **20** to afford the penultimate BIs **47**−**54**, respectively. Solvolytic removal of the *N*-BOC group as before then yielded the desired N-1,C-4-dialkylated BIs **55**−**62**, respectively (Scheme 5).

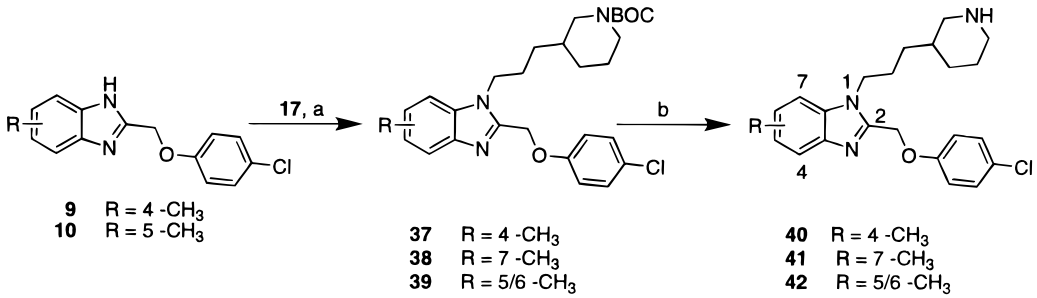
BIs **55**, **56**, **61**, and **62** are racemic, while **57**−**60** are each mixtures of two racemic diastereomers. The four constituent stereoisomers of the diaminoalkylated BI **60** were prepared using the *S*- and *R*-isomers of bromide **17**. The requisite isomers of **17** were prepared in seven steps from commercially available 3-pyridinecarboxaldehyde **(63)** as shown in Scheme 6. Horner−Emmons reaction of **63** with the sodium salt of triethyl phosphonoacetate gave pyridine **64**, which afforded piperidine **65** after hydrogenation. Classical resolution of **65** by salt formation with (*S*)-(+)- or (*R*)-(−)-mandelic acid yielded (*R*)- or (*S*)-**66**, respectively. The Mandelic acid salts (*R*)- or (*S*)-**66** were then converted to the free

**Scheme 2**[a]




[a] Key: (a) NaH, KI, DMF, 80 °C; (b) TFA, $CH_2Cl_2$, rt.

**Scheme 3**[a]



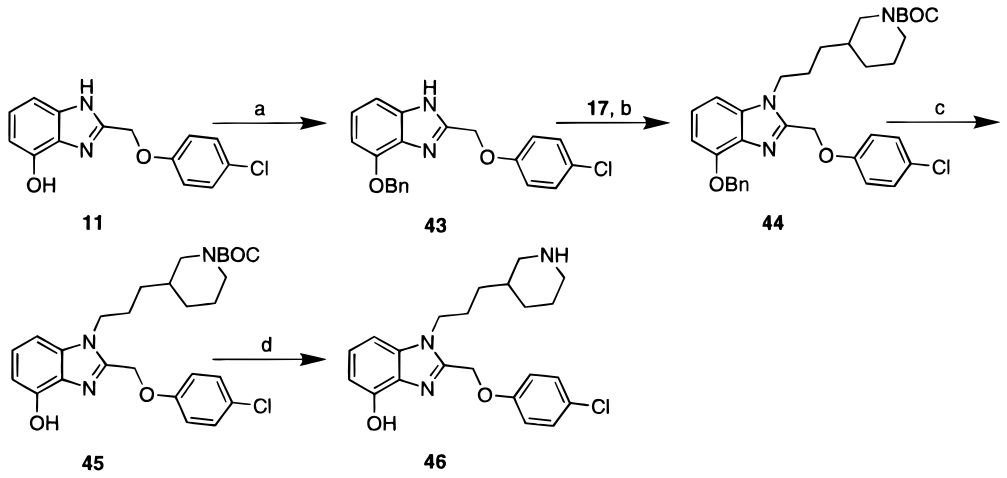

[a] Key: (a) NaH, KI, DMF, 80 °C; (b) TFA, $CH_2Cl_2$, rt.

amines (*R*)- or (*S*)-**65**, respectively. The enantiomeric purity of the resulting free amines was determined by conversion of either (*R*)- or (*S*)-**65** to its corresponding Mosher's amide ((*S*)-(−)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride, $Et_3N$, THF, 0 °C). Capillary GC[29] analysis of the corresponding amides showed the optical purity of each enantiomer to be greater than 99%. The absolute configuration of (*R*)-**66** was determined by an X-ray crystallograph of this salt, wherein the known configuration of mandelic acid could be used to determine the stereochemistry at C-3 of the piperidine. Protection of the amine functionality with di-*tert*-butyl dicarbonate gave the desired *N*-BOC piperidine (*R*)- or (*S*)-**67**. Selective reduction of the ester moiety with lithium aluminum hydride afforded the primary alcohol (*R*)- or (*S*)-**68**, respectively, which was treated with bromine and triphenylphosphine in dichloromethane to afford the desired bromides (*R*)- or (*S*)-**17**, respectively. Intermediate **45** was prepared in nonracemic form by reacting **43** with either (*R*)- or (*S*)-**17**, as described in Scheme 4. Each isomer of **45** was reacted with either *R*- or *S*-**17**, as described in Scheme 5, to afford (*S*,*S*)-**69**, (*R*,*R*)-**70**, (*S*,*R*)-**71**, and (*R*,*S*)-**72** (Chart 2). The convention we used to designate stereochemistry for **69**−**72** was that the first letter refers to the configuration of the (3-piperidinyl)propyl group at N-1 and the second letter refers to the configuration of the (3-piperidinyl)propyl group at C-4.

## Pharmacology

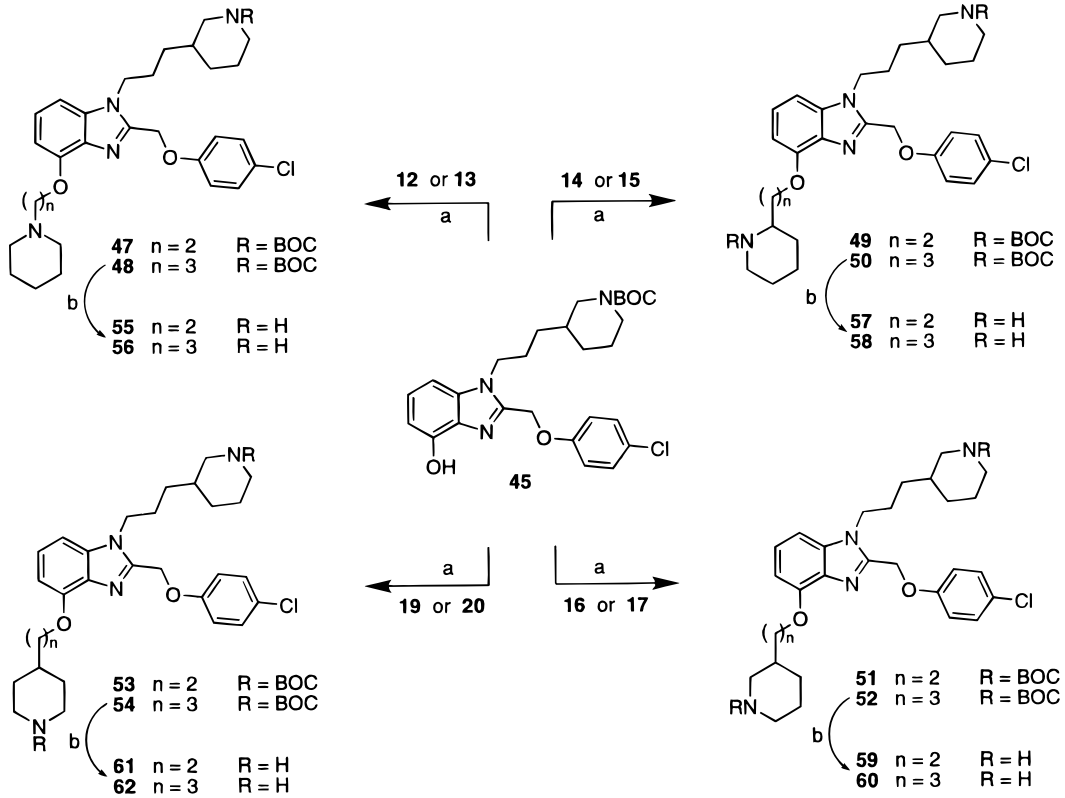
Affinity of the BIs for the Y1 receptor was determined by measuring their ability to displace [$^{125}$I]peptide YY binding to cloned human Y1 receptors expressed in AV-12 cells.[30] These data are presented in Table 1 and are expressed as $K_i$'s ($\mu$M). Affinity of some selected analogues for human NPY Y2, Y4, and Y5 receptors expressed in CHO cells was also determined using [$^{125}$I]-peptide YY binding (data not shown, all $K_i$'s > 1 $\mu$M). In vitro functional activity of selected compounds was determined by their ability to antagonize 1 nM NPYs inhibition of forskolin-stimulated cyclic AMP accumulation in SK-N-MC cells.[31] Cyclic AMP was quantified

**Scheme 4**[a]




[a] Key: (a) $PhCH_2OH$, $Ph_3P$, DEAD, THF, rt; (b) NaH, KI, DMF, 80 °C; (c) $H_2$, 5% Pd−C, EtOAc, rt; (d) TFA, $CH_2Cl_2$, rt.

**Scheme 5**[a]




[a] Key: (a) NaH, KI, DMF, 80 °C; (b) TFA, $CH_2Cl_2$, rt.

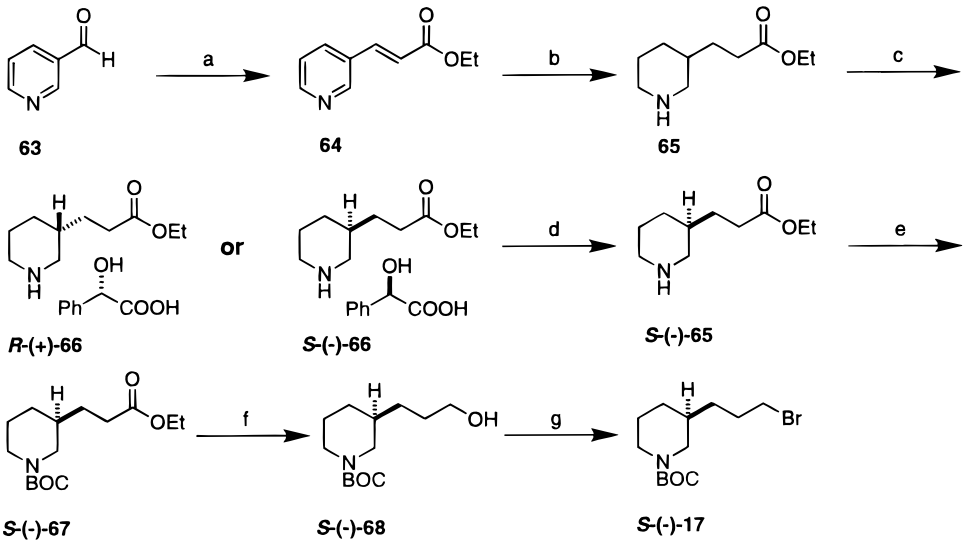
using either the Alvarez[32] method or a radioimmune assay (Amersham Corp). These data are also shown in Table 1.

## Results and Discussion

Our initial objective in this SAR was to explore the viability of the BI platform compared to indole for the discovery of Y1 antagonists. Next, we wanted to define the type of aminoalkyl substitution at N-1 that would optimize affinity of these ligands at the Y1 receptor. Following that, we hoped to increase affinity of these compounds by the appropriate addition of a second aminoalkyl substituent to the BI.

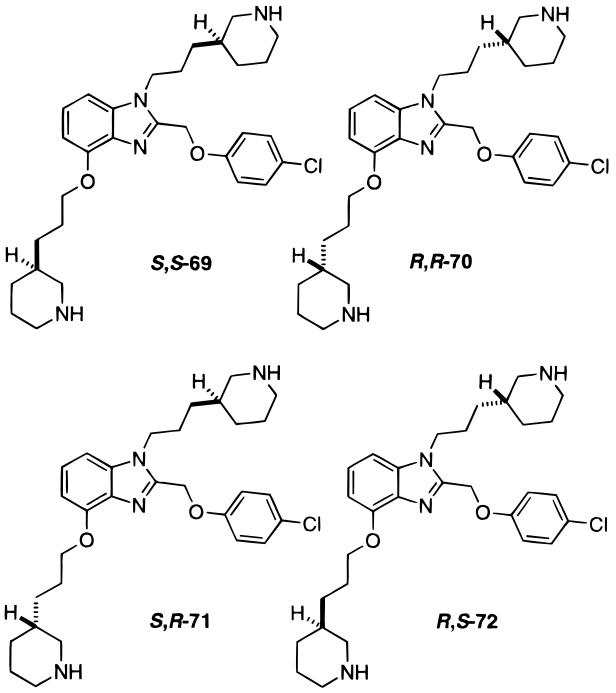
Among the other functionalities at N-1, piperidinyl alkyl groups resulted in more potent compounds. As shown in Table 1, 1-piperidine linked to the BI **8** via ethyl and propyl groups yielded compounds **21** and **22**. Compound **21** was essentially inactive, while **22** showed a very low Y1 receptor affinity ($K_i$ = 7.02 $\mu$M). Movement of the piperidine nitrogen to the 2 position using an ethyl (**30**) or propyl (**31**) linker failed to substantially increase receptor affinity. An increase in affinity was observed when N-1 was substituted with 3-piperidine through ethyl, propyl, and butyl spacers to generate **32**−**34**. Affinity was maximized with a propyl tether (**33**, $K_i$ = 0.70 $\mu$M). To complete this aspect of our study, compounds **35** and **36** were prepared that linked a 4-piperidine to the BI via ethyl and propyl groups. Both compounds showed approximately 1 $\mu$M affinity at the Y1 receptor. Among all of the above BIs, **33** with a 3-(3-

**Scheme 6**[a]




[a] Key: (a) $Et_2O_3PCH_2CO_2Et$, NaH, THF, 0 °C to rt; (b) $H_2$, $Rh/Al_2O_3$, EtOH, 60 psi, 60 °C; (c) (*R*)-(−)- or (*S*)−(+)-Mandelic Acid, EtOAc, 70 °C; (d) $K_2CO_3$, EtOAc, rt; (e) $(BOC)_2O$, $K_2CO_3$, $THF/H_2O$, rt; (f) $LiAlH_4$, $Et_2O$, rt; (g) $Br_2$, $PPh_3$, pyridine, $CH_2Cl_2$, 0 °C to rt.

**Chart 2**




piperidinyl)propyl substituent at N-1 demonstrated the highest Y1 receptor affinity, and this compound was chosen for subsequent SAR studies.

To further increase Y1 receptor affinity, we took advantage of the known SAR of NPY (the two C-terminal arginines are vital for the high affinity of NPY). We had hoped to mimic NPY's interaction in the BI series by incorporating an additional aminoalkyl functionality. We incorporated a methyl group on the aromatic ring as a probe to identify the best position to substitute with an additional aminoalkyl group. To this end, we prepared the methyl-substituted BIs **40**−**42**. The 4-methyl analogue **40** showed a 7-fold higher affinity than the parent BI **33**, while methyl substitution at C-7, **41**, gave only a 2-fold increase in affinity compared to **33**. Substitution at either C-5 or C-6 resulted in the less potent BI **42**.

On the basis of the above observations, we chose to probe for a second amine recognition domain with the BIs through incorporation of aminoalkyl functionality at C-4. We selected the use of oxygen as a link to the aminoalkyl group because this appeared more opera-

**Table 1.** In Vitro Binding Affinity of Benzimidazoles at the NPY Y1 Receptor in AV-12 Cell Line. In Vitro Functional Activity (cAMP) of Benzimidazole **55**, **56**, **58**−**62**, and **69**−**72** in SK-N-MC Cell Line

| compd | $K_i$ ($\mu$M)[a−c] AV-12 human Y1 | $K_i$ ($\mu$M)[c,d] SK-N-MC cells (cAMP) |
|---|---|---|
| **1 (BIBP3226)** | 0.0046 ± 0.0003 | 0.011 |
| **2** | 2.31 ± 0.193 | |
| **21** | >100 | |
| **22** | 7.02 ± 1.02 | |
| **30** | 7.86 ± 0.12 | |
| **31** | 3.23 ± 0.76 | |
| **32** | 1.28 ± 0.11 | |
| **33** | 0.70 ± 0.13 | |
| **34** | 1.21 ± 0.06 | |
| **35** | 0.94 ± 0.02 | |
| **36** | 0.98 ± 0.02 | |
| **40** | 0.097 ± 0.002 | |
| **41** | 0.400 ± 0.10 | |
| **42** | 1.29 ± 0.10 | |
| **46** | 5.30 ± 0.25 | |
| **55** | 0.043 ± 0.0013 | 0.240 |
| **56** | 0.0017 ± 0.000 03 | 0.0027 |
| **57** | 0.029 ± 0.0016 | |
| **58** | 0.016 ± 0.0002 | 0.053 |
| **59** | 0.018 ± 0.0001 | 0.091 |
| **60** | 0.030 ± 0.0003 | 0.077 |
| **61** | 0.007 ± 0.0003 | 0.015 |
| **62** | 0.152 ± 0.014 | 0.119 |
| (*S*,*S*)-**69** | 0.006 ± 0.0003 | 0.087 |
| (*R*,*R*)-**70** | 0.041 ± 0.003 | 0.153 |
| (*R*,*S*)-**71** | 0.027 ± 0.001 | 0.137 |
| (*S*,*R*)-**72** | 0.017 ± 0.0004 | 0.065 |

[a] In vitro binding affinity in AV-12 cells is measured by the method described in ref 30. [b] Compounds **55**, **56**, **57**, **58**, **61**, (*S*,*S*)-**69**, (*R*,*R*)-**70**, (*R*,*S*)-**71**, and (*S*,*R*)-**72** were tested at the Y2, Y4, and Y5 receptors and had $K_i$ values >1 $\mu$M. The method of assay is described in ref 30. [c] Each number represents two measurement ($n$ = 2). [d] In vitro functional assay (cAMP) in SK-N-MC is measured by the method described in refs 31 and 32.

tionally feasible. This strategy led to the synthesis of the BIs **55**−**62**. Among these new diaminoalkylated BIs, **56** with a (1-piperidinyl)propyl substituent showed the highest Y1 receptor affinity ($K_i = 0.0017$ $\mu$M), while its truncated ethyl analogue, **55**, showed a lower affinity ($K_i = 0.043$ $\mu$M). The 2-piperidine linked BIs, **57** and **58**, demonstrated equivalent affinity for the receptor though significantly less than **56**. The 3-piperidine analogous **59** and **60** also had similar but lower affinity than **56**. On the other hand, the 4-piperidine BIs **61** and **62** showed very different Y1 receptor affinities, and the ethyl-linked 4-piperidine analogue (**61**) demonstrated a very high affinity of $K_i = 0.007$ $\mu$M. The large differences in the affinity of BIs **56** and **62** show the importance of relative relationships of the two basic nitrogens in the diaminoalkylated BIs.

Synthesis and evaluation of isomers (**69**−**72**) of **60** showed only limited stereoselectivity for binding of **60**. The most potent one, (*S*,*S*)-**69**, has a 7-fold higher affinity than the mixtures of isomers, **60**. Relative affinity of the stereoisomers followed the order of *S*,*S* > *S*,*R* > *R*,*S* > *R*,*R*. The fact that these stereoisomers are not distinctly different may stem from a lack of significant differentiation between the two piperidine isomers. One could envision that each enantiomer could interact with the amine recognition domain in the Y1 receptor in a similar fashion. In this process, each enantiomer would occupy a similar area in space.

As shown in Table 1, benzimidazoles **55**, **56**, **58**−**62**, and **69**−**72** were evaluated in an assay for functional activity at Y1 receptor. All demonstrated antagonist activity at the Y1 receptor by reversing the NPY-induced inhibition of forskolin-stimulated cAMP. The differences between the binding and functional data remain to be determined but may be due to the fact that in the binding assay, affinity was measured under equilibrium conditions; whereas in the functional assay, the agonist (NPY) and antagonists were added at the same time and incubated for only 15 min due to the receptor desensitization with prolonged stimulation.

Selected Y1 antagonists such as **55**−**58**, **61**, and **69**−**72** were tested for affinity to human Y2, Y4, and Y5 receptors expressed in CHO cells. These BIs showed less than 30% inhibition of the binding of peptide YY at a concentration of 1 $\mu$M at these receptors. Thus, these compounds bind to the NPY Y1 receptor with high selectivity.

Hipskind et al. recently published a series of indole NPY Y1 antagonists.[26] They showed that the (4-chlorophenoxy)methyl group was an optimal C-2 substituent on the indole nucleus for Y1 binding affinity. This is consistent with what we have observed in the BI series. As shown in Figure 1, 3-(3-piperidinyl)propyl is also the optimal N-1 substituent for both BI **56** and indole **3**. On the basis of these two common structural elements, we believe that the N-1 positions of each series overlap with one another. However, while both series require at least two basic amine functionalities for high binding affinity at the Y1 receptor, the nature of the second aminoalkyl group and its point of attachment to the heteroaromatic ring system is distinctly different, Figure 1. This may suggest that the aminoalkyl groups attached to the C-3 position of indole-based NPY antagonists and the C-4 position of the BI-based antagonists interact with different binding domain at the Y1 receptor.

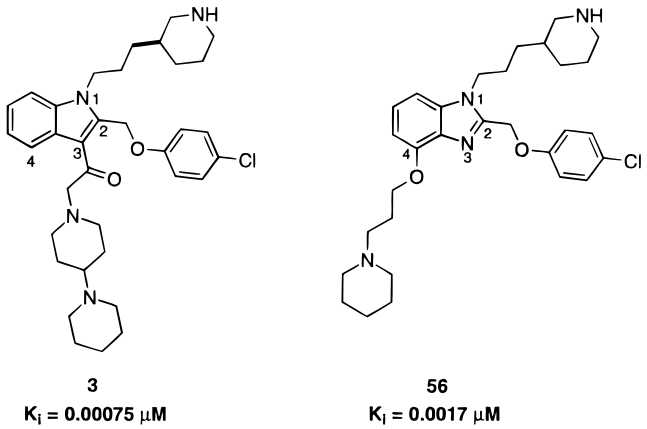



**Figure 1.** Structures of indole **3** and benzimidazole **56**.

## Summary

A series of 2-[(4-chlorophenoxy)methyl]benzimidazoles substituted at the N-1 and C-4 positions were prepared and characterized as Y1 receptor antagonists. Substitution at N-1 was optimized with a 3-(3-piperidinyl)-propyl substituent, and the relative orientation of the basic nitrogen and the BI nuclei was important for receptor affinity. Introduction of a second aminoalkyl functionality in the BI structure at C-4 and the relative spatial relationships of the basic amines markedly affected Y1 receptor affinity. The N-1, 3-(3-piperidinyl)-propyl and C-4, [3-(1-piperidinyl)propyl]oxy **56** with affinity of $K_i = 0.0017$ $\mu$M represents a 1360-fold increase in activity over the lead indole **2** with $K_i = 2.3$ $\mu$M. The very high receptor affinity achieved with the diamine-substituted BI and the observed SAR in this series suggests that the amines in the BIs may be binding similarly to the two C-terminal arginines of NPY. The small differences in the binding affinity of **60** and its stereoisomers **69**−**72** showed only limited stereoselectivity for binding of **60** to the Y1 receptor. The BI antagonists discovered in this work, because of their high affinities for the Y1 receptor, represent important new tools for understanding activities mediated through the Y1 receptor.

## Experimental Section

**General Methods.** Reagents used were the highest quality available commercially. Reaction solvents were anhydrous. All reactions were carried out under a positive pressure of dry nitrogen. Temperatures refer to the temperature of the bath into which the reaction vessel is immersed. Sodium hydride refers to 60 wt % sodium hydride (Aldrich) that was washed with hexane prior to use. All other solvents and reagents were used as obtained. "Workup" refers to addition to the reaction mixture of a neutral or basic aqueous solution, separation of the organic layer, and then extraction of the aqueous layer *n* times (×) with the indicated solvent. The combined organic extracts were dried over $Na_2SO_4$, filtered, concentrated in a vacuum, and purified as indicated. "Chromatography" refers to flash chromatography on 230−400 mesh silica gel 60. The reactions were generally monitored for completion using thin-layer chromatography (TLC). Analytical gas chromatography (GC) was performed on a Hewlett-Packard 5890 series 11 gas chromatograph utilizing an Ultra 2 (cross-linked 5% PhMe silicone) capillary column (25 m × 0.32 mm × 0.52 $\mu$m film thickness). $^1$H NMR spectra were obtained on a GE QE-300

or Brocker 300 spectrometer. Elemental analyses for carbon, hydrogen, and nitrogen were determined on a Control Equipment Corp. 440 elemental analyzer. The amount of solvent present in the molecular formula was determined by $^1$H NMR and microanalysis. Optical rotations were obtained using the Perkin-Elmer 241 polarimeter and are reported at the sodium D line (589). The enantiomers of each compound were prepared using the same procedure as is described for the racemate. Each enantiomer gave identical $^1$H NMR spectrum as for the corresponding racemate.

**2-[(4-Chlorophenoxy)methyl]benzimidazole (8).** To a room-temperature solution of (4-chlorophenoxy)acetonitrile (25 g, 149 mmol) in methanol (475 mL) was added sodium methoxide (7.7 g, 143 mmol). After 1 h at room temperature, the reaction mixture was treated with 1,2-diaminobenzene dihydrochloride (25.9 g, 143 mmol). After 2 h at room temperature, water (300 mL) was poured into the reaction mixture. The precipitated product was isolated by filtration. This material was dried in a vacuum at 30 °C overnight to afford 35.2 g (91%) of **8** as a beige solid, mp 184−186 °C. Anal. ($C_{14}H_{11}ClN_2O$) C, H, N.

**2-[(4-Chlorophenoxy)methyl]-4-methylbenzimidazole (9).** To a room-temperature solution of (4-chlorophenoxy)-acetonitrile (2.68 g, 16 mmol) in methanol (52 mL) was added sodium methoxide (0.83 g, 15.4 mmol). After 30 min at room temperature, the reaction mixture was treated with 2,3-diaminotoluene dihydrochloride (3 g, 15.4 mmol). After 3 h at room temperature, the solvent was removed under vacuum. Workup: 2 × 30 mL of sodium bicarbonate/2 × 30 mL of water/2 × 30 mL of dichloromethane. The combined organic extract was condensed and dried in a vacuum at 30 °C overnight to afford 4.1 g (97%) of **9** as a light brown solid. Anal. ($C_{15}H_{13}ClN_2O$) C, H, N.

**2-[(4-Chlorophenoxy)methyl]-5-methylbenzimidazole (10).** As for **9**, 4.48 g (27.6 mmol) of (4-chlorophenoxy)-acetonitrile and 1.39 g (25.6 mmol) of sodium methoxide in dry methanol (270 mL) was treated with 5 g (25.6 mmol) of 3,4-diaminotoluene to afford 7 g (60%) of **10** as a beige solid. Anal. ($C_{15}H_{13}ClN_2O$) C, H, N.

**2-[(4-Chlorophenoxy)methyl]-4-hydroxybenzimidazole (11).** As for **9**, 1 g (6 mmol) of (4-chlorophenoxy)-acetonitrile and 0.31 g (5.7 mmol) of sodium methoxide in dry methanol (20 mL) was treated with 1.13 g (5.7 mmol) of 2,3-diaminophenol to afford 1.42 of **11** as a white solid. Anal. ($C_{14}H_{11}ClN_2O_2$) C, H, N.

**1-[2-(1-Piperidinyl)ethyl]-2-[(4-chlorophenoxy)-methyl]benzimidazole (21).** To a solution of **8** (500 mg, 2.04 mmol) in dimethylformamide (10 mL) was added sodium hydride (98 mg, 2.4 mmol). After 30 min at room temperature, the reaction mixture was treated with the hydrochloride salt of the 2-(1-piperidinyl)ethyl chloride (442 mg 2.4 mmol), potassium carbonate (422 mg, 3.06 mmol), and potassium iodide (68 mg, 0.41 mmol). The reaction mixture was heated to 80 °C for 3 h. The mixture was cooled to room temperature. Workup: 3 × 20 mL of water/2 × 20 mL of ether. The combined organic layer was dried, concentrated, and subjected to chromatography (0:30:70%−5:35:60% triethylamine/ethyl acetate/hexanes two-step gradient) to afford 543.3 mg (72%) of **21** as a white solid. Anal. ($C_{21}H_{24}ClN_3O$) C, H, N.

**1-[3-(1-Piperidinyl)propyl]-2-[(4-chlorophenoxy)methyl]benzimidazole (22).** As for **21**, 300 mg (1.16 mmol) of **8**, 56 mg (1.39 mmol) of sodium hydride, 275 mg (1.39 mmol) of the hydrochloride salt of the 3-(1-piperidinyl)propyl chloride, 240 mg (1.74 mmol) of potassium carbonate, and 38 mg (0.23 mmol) of potassium iodide in dimethylformamide (5 mL) gave 232 mg (52%) of **22** as a white solid. Anal. ($C_{22}H_{26}ClN_3O\cdot0.25H_2O$) C, H, N.

**1-[2-[*N*-(*tert*-Butyloxycarbonyl)-2-piperidinyl]ethyl]-2-[(4-chlorophenoxy)methyl]benzimidazole (23).** As for **21**, 200 mg (0.97 mmol) of **8**, 46 mg (1.19 mmol) of sodium hydride, 339 mg (1.16 mmol) 2-[*N*-*tert*-butyloxycarbonyl)-2-piperidinyl]-ethyl bromide, and 32 mg (0.19 mmol) of potassium iodide in dimethylformamide (5 mL) gave 394.2 mg (86%) of **23** as a white solid, mp 135−136 °C. Anal. ($C_{26}H_{32}ClN_3O_3$) C, H, N.

**1-[3-[*N*-(*tert*-Butyloxycarbonyl)-2-piperidinyl]propyl]-2-[(4-chlorophenoxy)methyl]benzimidazole (24).** As for **21**, 200 mg (0.77 mmol) of **8**, 38 mg (0.93 mmol) of sodium hydride, 285 mg (0.93 mmol) of 3-[*N*-(*tert*-butyloxycarbonyl)-2-piperidinyl]propyl bromide, and 26 mg (0.15 mmol) of potassium iodide in dimethylformamide (3 mL) gave 203 mg (54%) of **24** as a white solid. Anal. ($C_{27}H_{34}ClN_3O_3$) C, H, N.

**1-[2-[*N*-(*tert*-Butyloxycarbonyl)-3-piperidinyl]ethyl]-2-[(4-chlorophenoxy)methyl]benzimidazole (25).** As for **21**, 300 mg (1.16 mmol) of **8**, 56 mg (1.39 mmol) of sodium hydride, 38 mg (0.23 mmol) of potassium iodide, and 406 mg (1.39 mmol) of 2-[*N*-(*tert*-butyloxycarbonyl)-3-piperidinyl]ethyl bromide in dimethylformamide (5 mL) gave 409 mg (75%) of **25** as a white solid. Anal. ($C_{26}H_{32}ClN_3O_3\cdot0.75H_2O$) C, H, N.

**1-[3-[*N*-(*tert*-Butyloxycarbonyl)-3-piperidinyl]propyl]-2-[(4-chlorophenoxy)methyl]benzimidazole (26).** As for **21**, 300 mg (1.16 mmol) of **8**, 56 mg (1.39 mmol) of sodium hydride, 38 mg (0.23 mmol) of potassium iodide, and 425 mg (1.39 mmol) of 3-[*N*-(*tert*-butyloxycarbonyl)-3-piperidinyl]propyl bromide in dimethylformamide (5 mL) gave 444 mg (79%) of **26** as a white solid, mp 101−103 °C. Anal. ($C_{27}H_{34}ClN_3O_3$) C, H, N.

**1-[4-[*N*-(*tert*-Butyloxycarbonyl)-3-piperidinyl]butyl]-2-[(4-chlorophenoxy)methyl]benzimidazole (27).** As for **21**, 100 mg (0.39 mmol) of **8**, 18.5 mg (0.46 mmol) of sodium hydride, 13 mg (0.08 mmol) of potassium iodide, and 214.5 mg (0.46 mmol) of 4-[*N*-(*tert*-butyloxycarbonyl)-3-piperidinyl]butyl bromide in dimethylformamide (2 mL) gave 248 mg (99%) of **27** as a white solid. Anal. ($C_{28}H_{36}ClN_3O_3$) C, H, N.

**1-[2-[*N*-(*tert*-Butyloxycarbonyl)-4-piperidinyl]ethyl]-2-[4-chlorophenoxy)methyl]benzimidazole (28).** As for **21**, 400 mg (1.55 mmol) of **8**, 74 mg (1.85 mmol) of sodium hydride, 51 mg (0.31 mmol) of potassium iodide, and 540 mg (1.85 mmol) of 2-[*N*-(*tert*-butyloxycarbonyl)-4-piperidinyl]ethyl bromide in dimethylformamide (6 mL) gave 633 mg (87%) of **28** as a white solid, mp 98−100 °C. Anal. ($C_{26}H_{32}ClN_3O_3$) C, H, N.

**1-[3-[*N*-(*tert*-Butyloxycarbonyl)-4-piperidinyl]propyl]-2-[(4-chlorophenoxy)methyl]benzimidazole (29).** As for **21**, 200 mg (0.77 mmol) of **8**, 38 mg (0.93 mmol) of sodium hydride, 26 mg (0.15 mmol) of potassium iodide, and 285 mg (1.39 mmol) 3-[*N*-(*tert*-butyloxycarbonyl)-4-piperidinyl]propyl bromide in dimethylformamide (3 mL) gave 357 mg (96%) of **29** as a white solid. Anal. ($C_{27}H_{34}ClN_3O_3\cdot0.5H_2O$) C, H, N.

**1-[2-(2-Piperidinyl)ethyl]-2-[(4-chlorophenoxy)-methyl]benzimidazole Trifluoroacetate (30).** A room-temperature solution of **23** (200 mg, 0.42 mmol) in dichloromethane (2 mL) was treated with trifluoroacetic acid (2 mL). After 1 h at room temperature, the reaction mixture was concentrated. Workup: 2 × 5 mL of water/3 × 5 mL of ether. The combined aqueous layer was dried under the freeze-dry system to afford 206 mg (93%) of **30** as a white solid, mp 146−147.5 °C. Anal. ($C_{23}H_{25}ClF_3N_3O_3\cdot0.75H_2O$) C, H, N.

**1-[3-(2-Piperidinyl)propyl]-2-[(4-chlorophenoxy)methyl]benzimidazole Trifluoroacetate (31).** As for **30**, 200 mg (0.41 mmol) of **24** and trifluoroacetic acid (2 mL) in dichloromethane (2 mL) gave 180 mg (88%) of **31** as a white solid. Anal. ($C_{24}H_{27}ClF_3N_3O_3$) C, H, N.

**1-[2-(3-Piperidinyl)ethyl]-2-[(4-chlorophenoxy)-methyl]benzimidazole Trifluoroacetate (32).** As for **30**, 200 mg (0.42 mmol) of **25** and trifluoroacetic acid (2 mL) in dichloromethane (2 mL) gave 190 mg (92%) of **32** as a white solid, mp 141−143 °C. Anal. ($C_{23}H_{25}ClF_3N_3O_3$) C, H, N.

**1-[3-(3-Piperidinyl)propyl]-2-[(4-chlorophenoxy)methyl]benzimidazole Trifluoroacetate (33).** As for **30**, 200 mg (0.41 mmol) of **26** and trifluoroacetic acid (2 mL) in dichloromethane (2 mL) gave 198 mg (96%) of **33** as a white solid. Anal. ($C_{24}H_{27}ClF_3N_3O_3$) C, H, N.

**1-[4-(3-Piperidinyl)butyl]-2-[(4-chlorophenoxy) methyl]benzimidazole Trifluoroacetate (34).** As for **30**, 130 mg (0.2 mmol) of **27** and trifluoroacetic acid (2 mL) in dichloromethane (1.5 mL) gave 98 mg (94%) of **34** as a white solid. Anal. ($C_{25}H_{29}ClF_3N_3O_3$) C, H, N.

**1-[2-(4-Piperidinyl)ethyl]-2-[(4-chlorophenoxy)methyl-]benzimidazole Trifluoroacetate (35).** As for **30**, 200 mg (0.42 mmol) of **28** and trifluoroacetic acid (2 mL) in dichloromethane (2 mL) gave 190 mg (92%) of **35** as a white solid, mp 155−157 °C. Anal. ($C_{25}H_{26}ClF_6N_3O_5$) C, H, N.

**1-[3-(4-Piperidinyl)propyl]-2-[(4-chlorophenoxy)methyl]benzimidazole Trifluoroacetate (36).** As for **30**, 350 mg (0.72 mmol) of **29** and trifluoroacetic acid (3 mL) in dichloromethane (3 mL) gave 354 mg (98%) of **36** as a white solid, mp 161−163 °C. Anal. ($C_{24}H_{27}ClF_3N_3O_3$) C, H, N.

**1-[3-[*N*-(*tert*-Butyloxycarbonyl)-3-piperidinyl]propyl]-2-[(4-chlorophenoxy)methyl]-4-methylbenzimidazole and 1-[3-[*N*-(*tert*-butyloxycarbonyl)-3-piperidinyl]propyl]-2-[(4-chlorophenoxy)methyl]-7-methylbenzimidazole (37 and 38).** As for 21, 200 mg (0.73 mmol) of 9, 35 mg (0.9 mmol) of sodium hydride, 275 mg (0.9 mmol) of 3-[*N*-(*tert*-butyloxycarbonyl)-3-piperidinyl]propyl bromide, and 24 mg (0.14 mmol) of potassium iodide in dimethylformamide (3 mL) gave 199 mg (55%) of 37 (Anal. ($C_{28}H_{36}ClN_3O_3 \cdot H_2O$) C, H, N) and 66 mg (18%) of 38, both as white solids. Anal. ($C_{28}H_{36}ClN_3O_3$) C, H, N.

**1-[3-[*N*-(*tert*-Butyloxycarbonyl)-3-piperidinyl]propyl]-2-[(4-chlorophenoxy)methyl]-5/6-methylbenzimidazole (39).** As for 21, 200 mg (0.73 mmol) of 10, 35 mg (0.9 mmol) of sodium hydride, 275 mg (0.9 mmol) of 3-[*N*-(*tert*-butyloxycarbonyl)-3-piperidinyl]propyl bromide, and 24 mg (0.14 mmol) of potassium iodide in dimethylformamide (3 mL) gave 132 mg (36%) of 39 as a 1:1 mixture of inseparable regioisomers. Anal. ($C_{28}H_{36}ClN_3O_3$) C, H, N.

**1-[3-(3-Piperidinyl)propyl]-2-[(4-chlorophenoxy)methyl]-4-methylbenzimidazole Trifluoroacetate (40).** As for **30**, 900 mg (1.81 mmol) of **37** and trifluoroacetic acid (5 mL) in dichloromethane (5 mL) gave 859 mg (93%) of **40** as a beige solid. Anal. ($C_{25}H_{29}ClF_3N_3O_3$) C, H, N.

**1-[3-(3-Piperidinyl)propyl]-2-[(4-chlorophenoxy)methyl]-7-methylbenzimidazole Trifluoroacetate (41).** As for **30**, 50 mg (0.1 mmol) of **38** and trifluoroacetic acid (1 mL) in dichloromethane (1 mL) gave 28 mg (54%) of **41** as a beige solid. Anal. ($C_{25}H_{29}ClF_3N_3O_3 \cdot 1.5H_2O$) C, H, N.

**1-[3-(3-Piperidinyl)propyl]-2-[(4-chlorophenoxy)methyl]-5/6-methylbenzimidazole Trifluoroacetate (42).** As for **30**, 120 mg (0.24 mmol) of **39** and trifluoroacetic acid (2 mL) in dichloromethane (2 mL) gave 125 mg (100%) of **42** as a beige solid. Anal. ($C_{27}H_{30}ClF_6N_3O_5$) C, H, N.

**2-[(4-Chlorophenoxy)methyl]-4-(benzyloxy)benzimidazole (43).** To a room-temperature solution of **11** (500 mg, 1.8 mmol) and triphenylphosphine (572 mg, 2.2 mmol) in tetrahydrofuran (18 mL) were added benzyl alcohol (236 mg, 2.2 mmol) and diethyl azodicarboxylate (380 mg, 2.2 mmol). After 6 h at room temperature, the solvent was removed under vacuum. Workup (3 × 20 mL water/3 × 20 mL ethyl acetate) and chromatography (0−40% ethyl acetate/hexanes four-step gradient) afforded 351 mg (53%) of the product **43** as a white solid. Anal. ($C_{21}H_{17}ClN_2O_2$) C, H, N.

**1-[3-[*N*-(*tert*-Butyloxycarbonyl)-3-piperidinyl]propyl]-2-[(4-chlorophenoxy)methyl]-4-(benzyloxy)benzimidazole (44).** As for **21**, 350 mg (0.96 mmol) of **43**, 46 mg (1.1 mmol) of sodium hydride, 32 mg (0.19 mmol) of potassium iodide, and 352 mg (1.1 mmol) of 3-[*N*-(*tert*-butyloxycarbonyl)-3-piperidinyl]propyl bromide in dimethylformamide (4 mL) gave 250 mg (44%) of **44** as a white solid. Anal. ($C_{34}H_{40}ClN_3O_4$) C, H, N.

**1-[3-[*N*-(*tert*-Butyloxycarbonyl)-3-piperidinyl]propyl]-2-[(4-chlorophenoxy)methyl]-4-hydroxybenzimidazole (45).** A room-temperature solution of **44** (245 mg, 0.42 mmol) in dry ethyl acetate (5 mL) was degassed and then was treated with 5% Pd−C (245 mg). The reaction was stirred at room temperature under an atmospheric pressure of hydrogen for 2 h. The reaction was filtered through a layer of Celite cake, and the catalyst was washed with warm ethyl acetate (3 × 10 mL). The filtrate was condensed under vacuum to provide 165 mg (78%) of the pure product **45** as a white solid. Anal. ($C_{27}H_{34}ClN_3O_4$) C, H, N.

**1-[3(*S*)-[*N*-(*tert*-Butyloxycarbonyl)-3-piperidinyl]propyl]-2-[(4-chlorophenoxy)methyl]-4-hydroxybenzimidazole ((*S*)-(−)-45):** 93% yield; $[\alpha]_D = -11°$ ($c = 1$, $CH_2Cl_2$). Anal. ($C_{27}H_{34}ClN_3O_4$) C, H, N.

**1-[3(*R*)-[*N*-(*tert*-Butyloxycarbonyl)-3-piperidinyl]propyl]-2-[(4-chlorophenoxy)methyl]-4-hydroxybenzimidazole ((*R*)-(+)-45):** 74% yield; $[\alpha]_D = +11°$ ($c = 1$, $CH_2Cl_2$). Anal. ($C_{27}H_{34}ClN_3O_4$) C, H, N.

**1-[3-(3-Piperidinyl)propyl]-2-[(4-chlorophenoxy)methyl]-4-hydroxybenzimidazole Trifluoroacetate (46).** As for **30**, 250 mg (0.5 mmol) of **45** and trifluoroacetic acid (2 mL) in dichloromethane (3 mL) gave 194 mg (75%) of **46** as a colorless semisolid material. Anal. ($C_{24}H_{27}ClF_3N_3O_4$) C, H, N.

**1-[3-[*N*-(*tert*-Butyloxycarbonyl)-3-piperidinyl]propyl]-2-[(4-chlorophenoxy)methyl]-4-[[2-(1-piperidinyl)ethyl]-oxy]benzimidazole (47).** A room-temperature solution of **45** (100 mg, 0.2 mmol) in dimethylformamide (2 mL) was treated with sodium hydride (10 mg, 0.24 mmol). After 30 min at room temperature, the reaction mixture was treated with the hydrochloride salt of the 2-(1-piperidinyl)ethyl chloride (44 mg, 0.24 mmol), potassium carbonate (41 mg, 0.3 mmol), and potassium iodide (7 mg, 0.04 mmol). The reaction mixture was heated at 80 °C for 3 h. The mixture was cooled to room temperature. Workup: 3 × 10 mL of water/2 × 10 mL of ether. The combined organic layer was dried, concentrated, and subjected to chromatography (0:40:60%−10:40:50% triethylamine/ethyl acetate/hexanes two-step gradient) to afford 109 mg (89%) of **47** as a white semisolid. Anal. ($C_{34}H_{47}ClN_4O_4 \cdot 1.5H_2O$) C, H, N.

**1-[3-[*N*-(*tert*-Butyloxycarbonyl)-3-piperidinyl]propyl]-2-[(4-chlorophenoxy)methyl]-4-[[3-(1-piperidinyl)propyl]-oxy]benzimidazole (48).** As for **47**, 100 mg (0.2 mmol) of **45**, 10 mg (0.24 mmol) of sodium hydride, 47 mg (0.24 mmol) of hydrochloride salt of the 3-(1-piperidinyl)propyl chloride, 41 mg (0.3 mmol) of potassium carbonate, and 7 mg (0.04 mmol) potassium iodide in dimethylformamide (2 mL) gave 101 mg (76%) of **48** as a colorless semisolid material. Anal. ($C_{35}H_{49}ClN_4O_4 \cdot 2H_2O$) C, H, N.

**1-[3-[*N*-(*tert*-Butyloxycarbonyl)-3-piperidinyl]propyl]-2-[(4-chlorophenoxy)methyl]-4-[[2-[*N*-(*tert*-butyloxycarbonyl)-2-piperidinyl]ethyl]oxy]benzimidazole (49).** As for **47**, 100 mg (0.2 mmol) of **45**, 10 mg (0.24 mmol) of sodium hydride, 70 mg (0.24 mmol) of 2-[*N*-(*tert*-butyloxycarbonyl)-2-piperidinyl]ethyl bromide, and 7 mg (0.04 mmol) of potassium iodide in dimethylformamide (2 mL) gave 108 mg (76%) of **49** as a colorless semisolid material. Anal. ($C_{39}H_{55}ClN_4O_6$) C, H, N.

**1-[3-[*N*-(*tert*-Butyloxycarbonyl)-3-piperidinyl]propyl]-2-[(4-chlorophenoxy)methyl]-4-[[3-(*N*-(*tert*-butyloxycarbonyl)-2-piperidinyl]propyl]oxy]benzimidazole (50).** As for **47**, 100 mg (0.2 mmol) of **45**, 10 mg (0.24 mmol) of sodium hydride, 74 mg (0.24 mmol) of 3-[*N*-(*tert*-butyloxycarbonyl)-2-piperidinyl]propyl bromide, and 7 mg (0.04 mmol) of potassium iodide in dimethylformamide (2 mL) gave 132 mg (91%) of **50** as a colorless semisolid material. Anal. ($C_{40}H_{57}ClN_4O_6$) C, H, N.

**1-[3-[*N*-(*tert*-Butyloxycarbonyl)-3-piperidinyl]propyl]-2-[(4-chlorophenoxy)methyl]-4-[[2-[*N*-(*tert*-butyloxycarbonyl)-3-piperidinyl]ethyl]oxy]benzimidazole (51).** As for **47**, 75 mg (0.15 mmol) of **45**, 8 mg (0.18 mmol) of sodium hydride, 53 mg (0.18 mmol) of 2-[*N*-(*tert*-butyloxycarbonyl)-3-piperidinyl]ethyl bromide, and 7 mg (0.04 mmol) of potassium iodide in dimethylformamide (2 mL) gave 32 mg (80%) of **51** as a colorless semisolid material. Anal. ($C_{39}H_{55}ClN_4O_6$) C, H, N.

**1-[3-[*N*-(*tert*-Butyloxycarbonyl)-3-piperidinyl]propyl]-2-[(4-chlorophenoxy)methyl]-4-[[3-[*N*-(*tert*-butyloxycarbonyl)-3-piperidinyl]propyl]oxy]benzimidazole (52).** As for **47**, 500 mg (1.8 mmol) of **11**, 160 mg (4 mmol) of sodium hydride, 1220 mg (4 mmol) of 3-[*N*-(*tert*-butyloxycarbonyl)-3-piperidinyl]propyl bromide, and 115 mg (0.72 mmol) of potas-

sium iodide in dimethylformamide (8 mL) gave 880 mg (67%) of **52** as a colorless semisolid material. Anal. ($C_{40}H_{57}ClN_4O_6$) C, H, N.

**(*S,S*)-1-[3(*S*)-[*N*-(*tert*-Butyloxycarbonyl)-3-piperidinyl]-propyl]-2-[(4-chlorophenoxy)methyl]-4-[[3(*S*)-[*N*-(*tert*-butyloxycarbonyl)-3-piperidinyl]propyl]oxy]benzimidazole ((*S,S*)-52).** As for **47**, 200 mg (0.73 mmol) of **11**, 64 mg (1.6 mmol) of sodium hydride, and 490 mg (1.6 mmol) of 3(*S*)-[*N*-(*tert*-butyloxycarbonyl)-3-piperidinyl]propyl bromide in dimethylformamide (3 mL) gave 248 mg (47%) of (*S,S*)-**52** as a colorless semisolid material. Anal. ($C_{40}H_{57}ClN_4O_6 \cdot 0.5H_2O$) C, H, N.

**(*R,R*)-1-[3(*R*)-[*N*-(*tert*-Butyloxycarbonyl)-3-piperidinyl]propyl]-2-[(4-chlorophenoxy)methyl]-4-[[3(*R*)-[*N*-(*tert*-butyloxycarbonyl)-3-piperidinyl]propyl]oxy]benzimidazole ((*R,R*)-52).** As for **47**, 200 mg (0.73 mmol) of **11**, 64 mg (1.6 mmol) of sodium hydride, and 490 mg (1.6 mmol) of 3(*R*)-[*N*-(*tert*-butyloxycarbonyl)-3-piperidinyl]propyl bromide in dimethylformamide (3 mL) gave 300 mg (57%) of (*R,R*)-**52** as a semisolid material. Anal. ($C_{40}H_{57}ClN_4O_6$) C, H, N.

**(*S,R*)-1-[3(*S*)-[*N*-(*tert*-Butyloxycarbonyl)-3-piperidinyl]-propyl]-2-[(4-chlorophenoxy)methyl]-4-[[3(*R*)-[*N*-(*tert*-butyloxycarbonyl)-3-piperidinyl]propyl]oxy]benzimidazole ((*S,R*)-52).** As for **47**, 200 mg (0.40 mmol) of (*S*)-**45**, 19 mg (0.48 mmol) of sodium hydride, and 147 mg (0.48 mmol) of 3(*R*)-[*N*-(*tert*-butyloxycarbonyl)-3-piperidinyl]propyl bromide in dimethylformamide (2 mL) gave 200 mg (69%) of (*S,R*)-**52** as a semisolid material. Anal. ($C_{40}H_{57}ClN_4O_6 \cdot 2H_2O$) C, H, N.

**(*R,S*)-1-[3(*R*)-[*N*-(*tert*-Butyloxycarbonyl)-3-piperidinyl]propyl]-2-[(4-chlorophenoxy)methyl]-4-[[3(*S*)-[*N*-(*tert*-butyloxycarbonyl)-3-piperidinyl]propyl]oxy]benzimidazole ((*R,S*)-52).** As for **47**, 75 mg (0.15 mmol) of (*R*)-**45**, 7 mg (0.18 mmol) of sodium hydride, and 55 mg (0.18 mmol) of 3(*S*)-[*N*-(*tert*-butyloxycarbonyl)-3-piperidinyl]propyl bromide in dimethylformamide (1 mL) gave 96 mg (88%) of (*R,S*)-**52** as a semisolid material. Anal. ($C_{40}H_{57}ClN_4O_6$) C, H, N.

**1-[3-[*N*-(*tert*-Butyloxycarbonyl)-3-piperidinyl]propyl]-2-[(4-chlorophenoxy)methyl]-4-[[2-[*N*-(*tert*-butyloxycarbonyl)-4-piperidinyl]ethyl]oxy]benzimidazole (53).** As for **47**, 100 mg (0.2 mmol) of **45**, 10 mg (0.24 mmol) of sodium hydride, 70 mg (0.24 mmol) of 2-[*N*-(*tert*-butyloxycarbonyl)-4-piperidinyl]ethyl bromide, and 7 mg (0.04 mmol) of potassium iodide in dimethylformamide (2 mL) gave 128 mg (90%) of **53** as a semisolid material. Anal. ($C_{39}H_{55}ClN_4O_6$) C, H, N.

**1-[3-[*N*-(*tert*-Butyloxycarbonyl)-3-piperidinyl]propyl]-2-[(4-chlorophenoxy)methyl]-4-[[3-[*N*-(*tert*-butyloxycarbonyl)-4-piperidinyl]propyl]oxy]benzimidazole (54).** As for **47**, 75 mg (0.15 mmol) of **45**, 8 mg (0.18 mmol) of sodium hydride, 55 mg (0.18 mmol) of 3-[*N*-(*tert*-butyloxycarbonyl)-4-piperidinyl]propyl bromide, and 7 mg (0.04 mmol) of potassium iodide in dimethylformamide (2 mL) gave 100 mg (92%) of **54** as a semisolid material. Anal. ($C_{40}H_{57}ClN_4O_6$) C, H, N.

**Tris[1-[3-(3-Piperidinyl)propyl]-2-[(4-chlorophenoxy)-methyl]-4-[[2-(1-piperidinyl)ethyl]oxy]benzimidazole] Trifluoroacetate (55).** As for **30**, 100 mg (0.14 mmol) of **47** and trifluoroacetic acid (2 mL) in dichloromethane (2 mL) gave 129 mg (93%) of **55** as a semisolid material. Anal. ($C_{35}H_{42}ClF_9N_4O_8$) C, H, N.

**Bis[1-[3-(3-Piperidinyl)propyl]-2-[(4-chlorophenoxy)-methyl]-4-[[3-(1-piperidinyl)propyl]oxy]benzimidazole] Trifluoroacetate (56).** As for **30**, 100 mg (0.2 mmol) of **48** and trifluoroacetic acid (2 mL) in dichloromethane (2 mL) gave 103 mg (85%) of **56** as a semisolid material. Anal. ($C_{34}H_{43}ClF_6N_4O_6$) C, H, N.

**Tris[1-[3-(3-Piperidinyl)propyl]-2-[(4-chlorophenoxy)-methyl]-4-[[2-(2-piperidinyl)ethyl]oxy]benzimidazole] Trifluoroacetate (57).** As for **30**, 30 mg (0.04 mmol) of **49** and trifluoroacetic acid (1 mL) in dichloromethane (1 mL) gave 27 mg (87%) of **57** as a semisolid material. Anal. ($C_{35}H_{42}ClF_9N_4O_8$) C, H, N.

**Bis[1-[3-(3-Piperidinyl)propyl]-2-[(4-chlorophenoxy)-methyl]-4-[[3-(2-piperidinyl)propyl]oxy]benzimidazole] Trifluoroacetate (58).** As for **30**, 80 mg (o.11 mmol) of **50** and trifluoroacetic acid (1.5 mL) in dichloromethane (1.5 mL) gave 71 mg (85%) of **58** as a semisolid material. Anal. ($C_{34}H_{43}ClF_6N_4O_6 \cdot 0.75H_2O$) C, H, N.

**Bis([-[3-(3-Piperidinyl)propyl]-2-[(4-chlorophenoxy)-methyl]-4-[[2-(3-piperidinyl)ethyl]oxy]benzimidazole] Trifluoroacetate (59).** As for **30**, 30 mg (0.04 mmol) of **51** and trifluoroacetic acid (0.5 mL) in dichloromethane (1 mL) gave 31 mg (100%) of **59** as a semisolid material. Anal. ($C_{33}H_{41}ClF_6N_4O_6$) C, H, N.

**Bis[1-[3-(3-Piperidinyl)propyl]-2-[(4-chlorophenoxy)-methyl]-4-[[3-(3-piperidinyl)propyl]oxy]benzimidazole] Trifluoroacetate (60).** As for **30**, 860 mg (1.2 mmol) of **52** and trifluoroacetic acid (5 mL) in dichloromethane (5 mL) gave 893 mg (100%) of **60** as a semisolid material. Anal. ($C_{34}H_{43}ClF_6N_4O_6$) C, H, N.

**Tris[1-[3-(3-Piperidinyl)propyl]-2-[4-chlorophenoxy)-methyl]-4-[[2-(4-piperidinyl)ethyl]oxy]benzimidazole] Trifluoroacetate (61).** As for **30**, 100 mg (0.14 mmol) of **53** and trifluoroacetic acid (2 mL) in dichloromethane (2 mL) gave 108 mg (91%) of **61** as a semisolid material. Anal. ($C_{35}H_{42}ClF_9N_4O_8$) C, H, N.

**Bis[1-[3-(3-Piperidinyl)propyl]-2-[(4-chlorophenoxy)-methyl]-4-[[3-(4-piperidinyl)propyl]oxy]benzimidazole] Trifluoroacetate (62).** As for **30**, 95 mg (0.13 mmol) of **54** and trifluoroacetic acid (2 mL) in dichloromethane (2 mL) gave 76 mg (77%) of **62** as a semisolid material. Anal. ($C_{34}H_{43}ClF_6N_4O_6$) C, H, N.

**3-Pyridylpropenoic Acid Ethyl Ester (64).** A solution of triethyl phosphonoacetate (100 g, 446 mmol) in tetrahydrofuran (500 mL) at 0 °C was treated with sodium hydride (17.4 g, 436 mmol) and stirred for 0.5 h. After being stirred for an additional 1 h at room temperature, this solution was cooled to 0 °C again and was treated with a solution of 3-pyridinecarboxaldehyde **63** (39 g, 363 mmol) in tetrahydrofuran (500 mL) gradually. After the reaction mixture was stirred at 0 °C for 3 h, it was allowed to warm to room temperature and stirred for an additional 6 h. Workup: 3 × 500 mL of water/2 × 500 mL of ethyl acetate. The combined organic layer was dried, concentrated, and subjected to chromatography (10−30% ethyl acetate/hexanes three-step gradient) to afford 62.5 g (97%) of the pure product **64**.

**3-(3-Piperidinyl)propionic Acid Ethyl Ester (65).** A solution of **64** (68 g, 379 mmol) in ethanol (500 mL) was treated with 5% rhodium on aluminum oxide (25 g). The mixture was kept under 60 psi of hydrogen at 60 °C for 12 h. The mixture was filtered through a layer of Celite. The filtrate was concentrated and subjected to chromatography (0−5% methanol/dichloromethane five-step gradient) to afford 60.7 g (87%) of the pure product **65**.

**3(*R*)-(3-Piperidinyl)propionic Acid Ethyl Ester Mandelic Acid Salt ((*R*)-(+)-66).** A solution of **65** (52 g, 281 mmol) in warm ethyl acetate (300 mL) was added to a solution of (*S*)-(+)-mandelic acid (42.7 g, 281 mmol) in warm ethyl acetate (300 mL). The mixture was mixed by stirring for 10 min. It was left at room temperature for 24 h. The resulting crystals were filtered, dried, and recrystallized again with ethyl acetate (300 mL). After 12 h, the salt crystals were filtered and subsequently dried to afford 47.4 g (50%) of very pure salt (*R*)-(+)-**66** as white crystals, $[\alpha]_D = +51.6°$ ($c = 1$, $CH_2Cl_2$).

**3(*S*)-(3-Piperidinyl)propionic Acid Ethyl Ester Mandelic acid ((*S*)-(−)-66).** A solution of **65** (27 g, 146 mmol) in warm ethyl acetate (150 mL) was added to a solution of (*R*)-(−)-mandelic acid (22.2 g, 146 mmol) in warm ethyl acetate (150 mL). The mixture was mixed by stirring for 10 min. It was left at room temperature for 24 h. The resulting crystals were filtered, dried, and recrystallized again with ethyl acetate (100 mL). After 12 h, the salt crystals were filtered and subsequently dried to afford 22.6 g (46%) of very pure salt (*S*)-(−)-**66** as white crystals, $[\alpha]_D = -49.9°$ ($c = 1$, $CH_2Cl_2$).

**3(*S*)-(3-Piperidinyl)propionic Acid Ethyl Ester ((*S*)-(−)-65).** A slurry of ((*S*)-(−)-**66**) salt (30 g, 89.1 mmol) in ethyl acetate (300 mmol) was treated with the aqueous solution of

potassium carbonate (300 mL of 10%). The free amine was extracted by ethyl acetate. The organic layer was washed with water (3 × 300 mL), dried, and concentrated in a vacuum to afford 16.5 g (100%) of the pure free amine (*S*)-(−)-**65** as a colorless oil, $[\alpha]_D = -8.5°$ ($c = 1$, $CH_2Cl_2$).

**3(*S*)-[*N*-(*tert*-Butyloxycarbonyl)-3-piperidinyl]propionic Acid Ethyl Ester ((*S*)-(−)-67).** A solution of (*S*)-(−)-**65** (9.2 g, 49.5 mmol) in a mixture of THF/$H_2O$ (250 mL; 1:1) was treated with potassium carbonate (8.2 g, 59.4 mmol) and di-*tert*-butyl dicarbonate (13 g, 59.4 mmol). The reaction mixture was stirred at room temperature for 6 h. Workup: 3 × 200 mL of water/2 × 200 mL of ethyl acetate. The combined organic layer was dried, concentrated, and subjected to chromatography (10−25% ethyl acetate/hexanes two-step gradient) to afford 14 g (99%) of the pure product (*S*)-(−)-**67** as a solid.

**3(*S*)-[*N*-(*tert*-Butyloxycarbonyl)-3-piperidinyl]propanol ((*S*)-(−)-68).** A room-temperature solution of (*S*)-(−)-**67** (13.2 9, 46.4 mmol) in ether (400 mL) was slowly treated with lithium aluminum hydride (1.8 g, 46.4 mmol). After being stirred at room temperature for 4 h, the reaction mixture was slowly poured into an aqueous solution of sodium hydroxide (200 mL, 15%). Workup: 3 × 200 mL of water/2 × 200 mL of ether. The combined organic layer was dried and concentrated to afford 10.2 g (91%) of alcohol (*S*)-(−)-**68** that was directly used in the next step.

**3(*S*)-[*N*-(*tert*-Butyloxycarbonyl)-3-piperidinyl]propyl Bromide ((*S*)-(−)-17).** A solution of triphenylphosphine (15.5 g, 59 mmol) in dichloromethane (170 mL) at 0 °C was treated with bromine until the solution turned pale yellow. To this mixture was added a solution of alcohol (*S*)-(−)-68 (10.2 g, 42.1 mmol) and pyridine (7.7 g, 59 mmol) in dichloromethane (50 mL). The reaction mixture was allowed to warm to room temperature and stirred for 6 h. Workup (3 × 200 mL of water/2 × 200 mL of ether). The combined organic layer was dried, concentrated, and subjected to chromatography (10% ethyl acetate/hexanes two-step gradient) to afford 9.5 g (73%) of the pure oily product (*S*)-(−)-17.

**Bis[(*S,S*)-1-[3(*S*)-(3-Piperidinyl)propyl]-2-[(4-chlorophenoxy)methyl]-4-[[3(*S*)-(3-piperidinyl)propyl]oxy]benzimidazole] Trifluoroacetate ((*S,S*)-69).** As for **30**, 240 mg (0.33 mmol) of (*S,S*)-**52** and trifluoroacetic acid (3 mL) in dichloromethane (3 mL) gave 242 mg (97%) of (*S,S*)-**69** as a semisolid material, $[\alpha]_D = -11.8°$ ($c = 1$, MeOH). Anal. ($C_{34}H_{43}ClF_6N_4O_6$) C, H, N.

**Bis[(*R,R*)-1-[3(*R*)-(3-Piperidinyl)propyl]-2-[(4-chlorophenoxy)methyl]-4-[[3(*R*)-(3-piperidinyl)propyl]oxy]benzimidazole] Trifluoroacetate ((*R,R*)-70).** As for **30**, 255 mg (0.35 mmol) of (*R,R*)-**52** and trifluoroacetic acid (3 mL) in dichloromethane (3 mL) gave 264 mg (100%) of (*R,R*)-**70** as a semisolid material, $[\alpha]_D = +12.8°$ ($c = 1$, MeOH). Anal. ($C_{34}H_{43}ClF_6N_4O_6$) C, H, N.

**Bis[(*S,R*)-1-[3(*S*)-(3-Piperidinyl)propyl]-2-[(4-chlorophenoxy)methyl]-4-[[3(*R*)-(3-piperidinyl)propyl]oxy]benzimidazole] Trifluoroacetate ((*S,R*)-71).** As for **30**, 195 mg (0.27 mmol) of (*S,R*)-**52** and trifluoroacetic acid (2 mL) in dichloromethane (3 mL) gave 155 mg (76%) of *S,R*-**71** as a semisolid material. $[\alpha]_D = +14.8°$ ($c = 1$, MeOH). Anal. ($C_{34}H_{43}ClF_6N_4O_6 \cdot 0.5H_2O$) C, H, N.

**Bis[(*R,S*)-1-[3(*R*)-(3-Piperidinyl)propyl]-2-[(4-chlorophenoxy)methyl]-4-[[3(*S*)-(3-piperidinyl)propyl]oxy]benzimidazole] Trifluoroacetate ((*R,S*)-72).** As for **30**, 90.5 mg (0.12 mmol) of (*R,S*)-**57** and trifluoroacetic acid (2 mL) in dichloromethane (2 mL) gave 90 mg (100%) of (*R,S*)-**72** as a semisolid material, $[\alpha]_D = -13.8°$ ($c = 1$, MeOH). Anal. ($C_{34}H_{43}ClF_6N_4O_6 \cdot 0.5H_2O$) C, H, N.

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**Supporting Information Available:** Combustion analysis for all final compounds and their immediate precursors, X-ray crystallography of (*R*)-(+)-**66**, and NMR spectra of more than 90% of the final products and their immediate precursors (18 pages). Ordering information is given on any current masthead page.

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