6-Substituted Benzimidazoles as New Nonpeptide Angiotensin II Receptor Antagonists: Synthesis, Biological Activity, and Structure-Activity Relationships

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Starting from the recently reported nonpeptidic angiotensin II (AII) receptor antagonists DuP 753 (1) and Exp 7711 (2), we have designed and investigated novel substituted benzimidazoles. Systematic variation of several substituents at the benzimidazole ring positions 4-7 led to the finding that substitution in position 6 with acylamino groups results in highly active AII antagonists. Compounds with 6-membered lactam or sultam substitutents in position 6 of benzimidazole showed receptor activities in the low nanomolar range but were only weakly active when given orally to rats. In contrast, analogous substitution of the benzimidazole moiety with basic heterocycles resulted in potent AII antagonists which were also well absorbed after oral application. The most active compound of this series, 33 (BIBR 277), was selected as a candidate for clinical development. On the basis of molecular modeling studies a binding model of this new class of AII antagonists to the AT1 receptor is proposed.

Introduction

The renin-angiotensin system (RAS) plays an important role in the control of blood pressure[1] and the regulation of volume and electrolyte homeostasis.[2] The therapeutic success of the angiotensin-converting enzyme inhibitors has demonstrated the advantage of pharmacological interference with the RAS in hypertension and congestive heart failure. This stimulated the search for additional pharmacological interventions with the RAS, namely renin inhibitors and AII receptor antagonists. Progress in the latter field has been made recently when Timmermans and his colleagues from DuPont de Nemours took up an earlier patent from Takeda[3] and developed orally active, nonpeptidic imidazole derivatives, which specifically and selectively interact with the AII receptors.[4,5] A particular advantage of these compounds is that they are devoid of intrinsic agonistic vasopressor activity, a common feature of the already known peptidic antagonists, which are structurally related to AII.[6,7] The antihypertensive activity of the nonpeptidic angiotensin antagonists has been demonstrated in various animal models of experimental hypertension.[8,9] The prototype and most advanced compound is losartan (DuP 753),[9] which is now in late clinical development.[10] Meanwhile other compounds structurally related to losartan have been synthesized.[11] In this report we describe the discovery of novel substituted benzimidazole derivatives[12] as well as structure-activity relationships, and we propose a model for the receptor binding of these new AII antagonists.

Chemistry

The compounds in Table I were synthesized as shown in Scheme I. The isomeric 4-/5-nitrobenzimidazoles 44a/ 44b were prepared by condensation of the respective diaminonitrobenzene with valeric acid in phosphorous oxychloride. Alkylation with the (bromomethyl)biphenyl
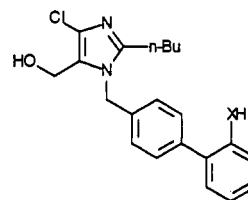
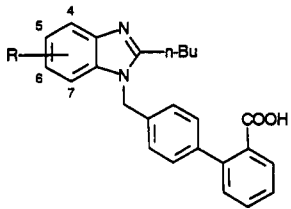1　XH = Tetrazol-5-yl (Losartan, DuP 753)

2　XH = COOH (EXP 7711)

derivative 45[13] in dimethyl sulfoxide using potassium *tert*-butoxide as base yielded 46a/46b as a mixture of the respective regioisomers. These could be easily separated by flash chromatography after hydrogenation of the nitro groups using Raney nickel as catalyst. Following this procedure the amino compounds 47b and 47c were obtained in a ratio of 55:45 and the 4- and 7-isomers (47a and 47d) in a ratio of 95:5. The intermediates 47a-d were converted into the corresponding acetamides by treatment with acetyl chloride or into the cyclohexylureas by reaction with cyclohexyl isocyanate. Finally the *tert*-butyl ester was cleaved by treatment with trifluoroacetic acid to yield the biphenylcarboxylic acids 8-19.

The preparation of the compounds in Table II is shown in Schemes II-IV. In order to introduce different alkylamino groups into the benzimidazole position 6, the chlorine-bearing intermediate 49 was prepared by reaction of 45 with 2-(valeroylamino)-4-chloronitrobenzene (48) (Scheme II). Nucleophilic substitution of the chlorine atom with primary or secondary amines at 130 °C gave the amino compounds 50a/50b. These were transformed into the benzimidazoles 20 and 21 by reduction of the nitro group followed by ring closure in glacial acetic acid and cleavage of the ester group as described before.

The tetrazole 28 was prepared as depicted in Scheme III. Selective protection of the 4-amino group in 51 with phthalic acid anhydride followed by acylation, reduction of the nitro group, and ring closure in glacial acetic acid yielded the benzimidazole 52. Alkylation of 52 with the trityl-protected biphenylyltetrazole 53[14] under the conditions described above resulted in a mixture of the 5-/

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● Abstract published in *Advance ACS Abstracts*, October 15, 1993.

Table I. Characterization and AT_1 Receptor Binding of Benzimidazoles, Substituted at the Phenylene Ring Positons 4–7
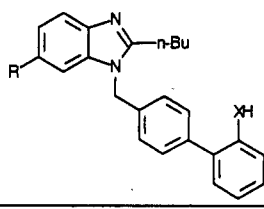

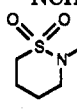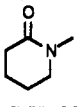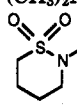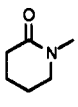| compd	R	mp, °C	formula[a]	IC$_{50}$, nM[b]
1 (DuP 753)				35
2 (EXP 7711)				350
3	H	214–215	$C_{25}H_{24}N_2O_2$	400
4	4-CH$_3$	260–262	$C_{26}H_{26}N_2O_2$	1200
5	5-CH$_3$	188–190 dec	$C_{26}H_{26}N_2O_2$	1200
6	6-CH$_3$	219–221	$C_{26}H_{26}N_2O_2$	850
7	7-CH$_3$	231–233	$C_{26}H_{26}N_2O_2 \cdot H_2O$	480
8	4-NH$_2$	268–270	$C_{25}H_{25}N_3O_2 \cdot H_2O$	1700
9	5-NH$_2$	64–66	$C_{25}H_{25}N_3O_2 \cdot 2CF_3COOH$	820
10	6-NH$_2$	72–74	$C_{25}H_{25}N_3O_2 \cdot 2CF_3COOH$	540
11	7-NH$_2$	251–254	$C_{25}H_{25}N_3O_2 \cdot 0.5H_2O$	1060
12	4-NHCOCH$_3$	280–283	$C_{27}H_{27}N_3O_3$	5700
13	5-NHCOCH$_3$	187–189	$C_{27}H_{27}N_3O_3 \cdot H_2O$	460
14	6-NHCOCH$_3$	252–254	$C_{27}H_{27}N_3O_3$	180
15	7-NHCOCH$_3$	243–248	$C_{27}H_{27}N_3O_3 \cdot 0.5H_2O$	1800
16	4-NHCONH-C$_6$H$_{11}$	242–244 dec	$C_{32}H_{36}N_4O_3$	29300
17	5-NHCONH-C$_6$H$_{11}$	176–177	$C_{32}H_{36}N_4O_3 \cdot CF_3COOH$	800
18	6-NHCONH-C$_6$H$_{11}$	199–200	$C_{32}H_{36}N_4O_3 \cdot CF_3COOH$	26
19	7-NHCONH-C$_6$H$_{11}$	278–279	$C_{32}H_{36}N_4O_3$	160

a All compounds exhibited NMR and mass spectra consistent with structure and gave satisfactory analyses C, H, N (±0.4%). *b* IC$_{50}$ for specific binding of [^{125}I]AII to rat lung membrane preparation. For details see the Experimental Section.

6-regioisomers, from which **54** could easily be obtained after removal of the protecting group and separation of the isomeric amino compounds by flash chromatography. Reaction of **54** with cyclohexyl isocyanate followed by treatment with hydrochloric acid yielded the deprotected tetrazole **28**.

The synthesis of benzimidazoles substituted with 6-membered sultams and lactams was achieved by acylation of the aminobenzimidazole **47e**, (prepared according to Scheme I) with 4-chloro-1-butanesulfonyl chloride[15] and subsequent treatment with sodium ethoxide (Scheme IV). The resulting sultam **55a** was treated with sodium azide and ammonium chloride at 140 °C to yield the tetrazole **31**. The lactam **32** was prepared in a similar manner starting from **47e** and 4-chlorovaleroyl chloride.

The compounds in Table III were prepared as shown in Schemes V–VII. For the synthesis of the benzimidazolyl-substituted benzimidazole **33** (Scheme V) methyl 4-amino-3-methylbenzoate (**56**) was acylated, nitrated in position 5, followed by reduction and ring closure to yield the benzimidazole **57**. After ester hydrolysis the resulting benzimidazole carboxylic acid was condensed with *N*-methyl-*o*-phenylenediamine in the presence of polyphosphorous acid to give the "double benzimidazole" **58**. Alkylation of **58** with **45** followed by ester cleavage yielded the carboxylic acid **33**. The 4-methyl group directed the biphenylylmethyl group into the benzimidazole position 1 to give the requisite regioisomer in large excess (ratio of

Table II. Effects of Benzimidazole Substituted with Alkylamino and Acylamino Residues in Position 6


compd	R	XH	mp, °C	formula[a]	IC$_{50}$, nM[b]
20	CH$_3$(CH$_2$)$_4$NH	COOH	108–113	$C_{30}H_{35}N_3O_2$	390
21	(piperidine)	COOH	199–200	$C_{30}H_{33}N_3O_2$	160
22	CH$_3$(CH$_2$)$_3$-CONH	COOH	253–255	$C_{30}H_{33}N_3O_3$	86
23	(CH$_3$)$_2$NCONH	COOH	198–200	$C_{28}H_{30}N_4O_3 \cdot CF_3COOH$	24
24	C$_6$H$_{11}$NHCON-CH$_3$	COOH	215–217	$C_{33}H_{38}N_4O_3$	26
25	CH$_3$(CH$_2$)$_2$SO$_2$-NCH$_3$	COOH	222–223	$C_{29}H_{33}N_3O_4S$	33
26	(sultam)	COOH	203–205	$C_{29}H_{31}N_3O_4S$	34
27	(lactam)	COOH	212–214	$C_{30}H_{31}N_3O_3$	81
28	C$_6$H$_{11}$NHCONH	tetrazole	232–234	$C_{32}H_{36}N_8O$	21
29	C$_6$H$_{11}$NHCON-CH$_3$	tetrazole	163–165	$C_{33}H_{38}N_8O \cdot H_2O$	10
30	(CH$_3$)$_2$NCONH	tetrazole	239–241	$C_{28}H_{30}N_8O$	8
31	(sultam)	tetrazole	189–191	$C_{29}H_{31}N_7O_2S$	3
32	(lactam)	tetrazole	163–165	$C_{30}H_{31}N_7O$	4

a All compounds exhibited NMR and mass spectra consistent with structure and gave satisfactory analyses C, H. N. (±0.4%). *b* IC$_{50}$ for specific binding of [^{125}I]AII to rat lung membrane preparation. For details see the Experimental Section.

1-/3-regioisomer = 95:5). The other analogues **34–36** and the benzoxazole-substituted benzimidazole **41** (Table III) were prepared in a similar manner.

The imidazopyridine-substituted benzimidazole **37** was prepared as shown in Scheme VI starting from the substituted acetophenone **59**. The latter was obtained by acylation of diethyl malonate with 4-(butyrylamino)-3-methylbenzoyl chloride[16] followed by decarboxylation and nitration (not shown). Side-chain bromination followed by condensation with 2-aminopyridine[17] and benzimidazole formation as described above yielded **60**. After alkylation with **45** and ester hydrolysis, the carboxylic acid **37** was obtained.

The starting material **61** for the synthesis of pyridine-substituted benzimidazoles like **39** was prepared from 3-bromotoluene and pyridine *N*-oxide.[18] Treatment of **61** with fuming nitric acid at low temperature gave a mixture of isomeric nitrophenyl compounds, from which the major product 2-(3-methyl-4-nitrophenyl)pyridine was easily obtained by crystallization. This intermediate was catalytically reduced and the resulting amino group was acylated. Nitration followed by reduction of the nitro group and ring closure in acetic acid gave the benzimidazole

Scheme I[a]
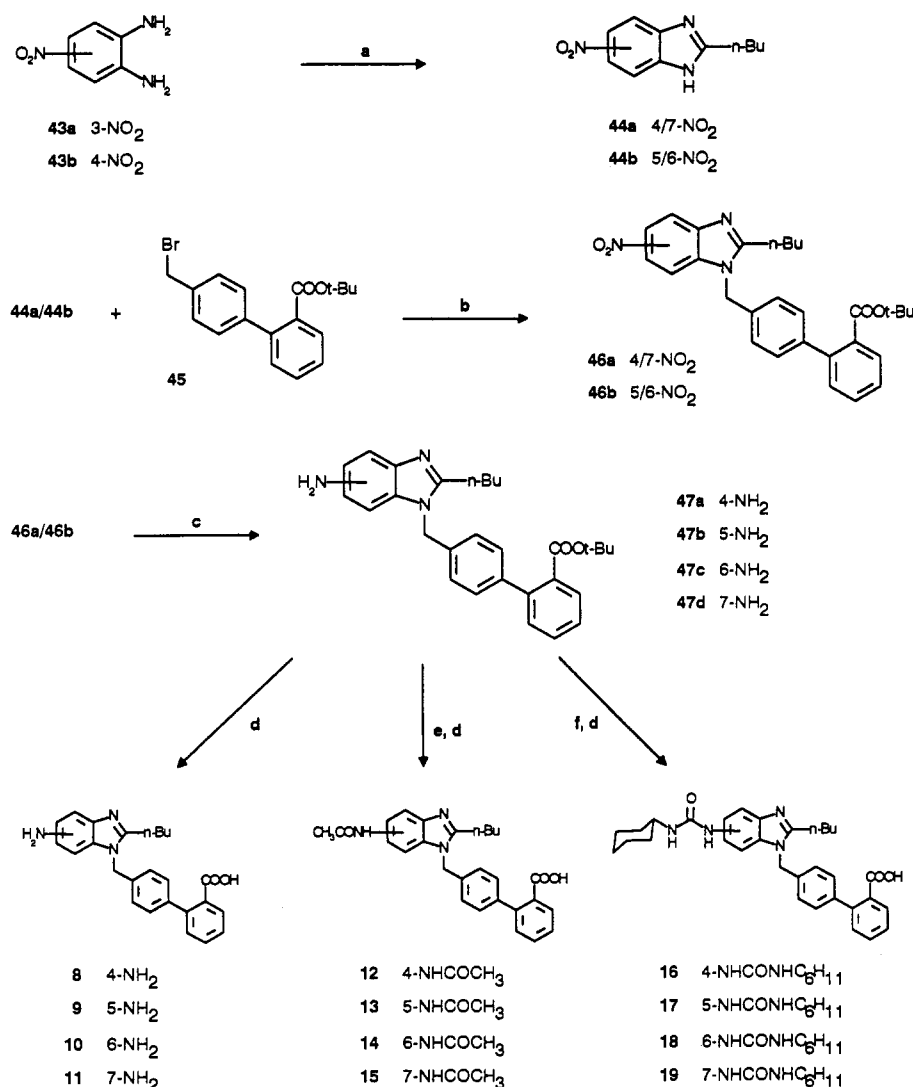
[a] (a) n-BuCOOH, POCl$_3$; (b) KOt-Bu, DMSO; (c) H$_2$, Ra-Ni, EtOH, 50 °C, 5 bar, chromatographic separation; (d) CF$_3$COOH, CH$_2$Cl$_2$; (e) CH$_3$COCl, pyr; (f) C$_6$H$_{11}$NCO, NEt$_3$, THF.
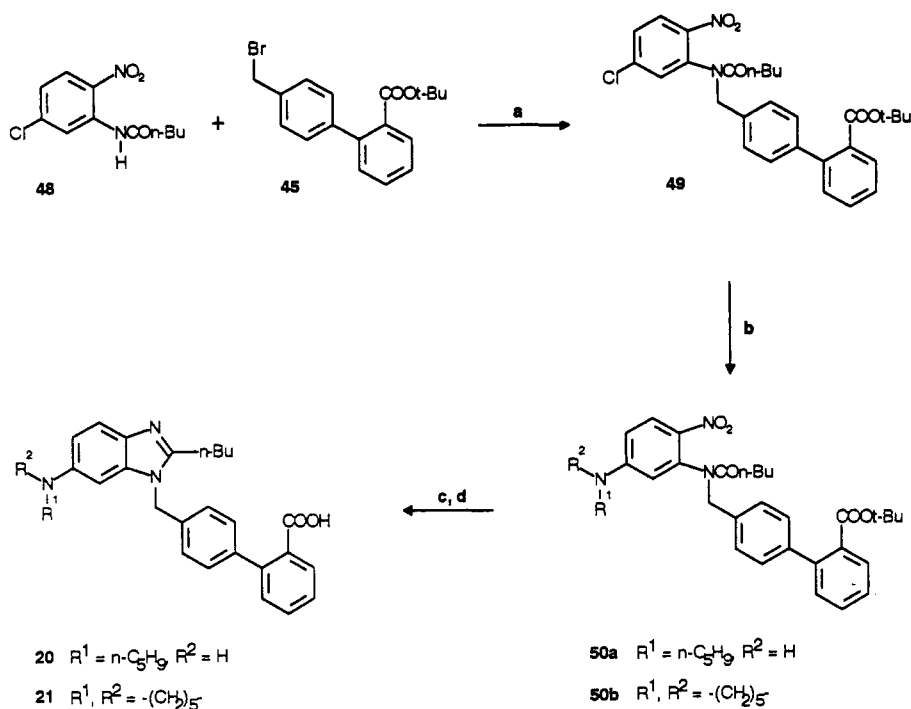
62. Alkylation of 62 with 53 and subsequent deprotection with hydrochloric acid yielded the tetrazole derivative 39.

Discussion

From the recently reported nonpeptide AII antagonists[5c,19] we chose the imidazole derivative 2 (EXP 7711) as a lead structure. In order find out the contribution of the heterocyclic moiety of compound 2 to receptor affinity, we prepared some simple heterocyclic analogs. These variations led to the finding that the substituted imidazole group could be replaced by 2-butylbenzimidazole (compound 3) without substantial loss of receptor affinity. This discovery has recently been confirmed by other groups.[11c,20] For example, benzimidazole derivatives with halogen atoms in position 5 or 6 as well as unsubstituted analogs have been described as weak AII antagonists.[11c] In order to gain deeper insight into structure–activity relationships, we prepared a series of benzimidazole analogs in which a set of substituents was systematically varied along the four phenylene ring positions 4–7 (Table I). We found that receptor affinity was not significantly influenced by small methyl and amino substituents, regardless of their position. However, acylation of the amino compounds resulted in considerable regioisomer-dependent differences in receptor binding. In case of the acetamides 12–15 the 4-isomer showed the lowest and the 6-isomer the highest

affinity (IC$_{50}$ = 5700 and 183 nM, respectively). This difference was even more pronounced in the series of the cyclohexylurea compounds 16–19 (29 300 and 26 nM for the 4- and 6-isomers, respectively). Obviously the more bulky substituents in position 4 are not tolerated by the receptor binding site. According to our binding model (see below) the formation of a hydrogen bond from the receptor to N-3 of the benzimidazole moiety is important for receptor affinity. This binding contribution is probably prevented by the bulky substituents in position 4. In contrast, the same substituents in position 6 (compounds 14 and 18) seem to contribute additional binding energy. The IC$_{50}$ values of the 5- and 7-isomers (compounds 13, 15, 17, and 19) were fairly similar to that of the unsubstituted benzimidazole (3) which indicates that there are areas at the receptor binding site tolerating these substituents. Compound 18 (BIBS 39)[21] is approximately 16-fold more potent as compared to the unsubstituted benzimidazole compound 3. In order to find out which part of the cyclohexylurea substituent might contribute to receptor binding, a series of analogous benzimidazoles substituted in position 6 were designed (Table II).

In contrast to the amino compounds 20 and 21, the acylated analogs 22–24 showed increased potency by about 1 order of magnitude. The increased binding energy is probably a result of an additional hydrogen bond with the
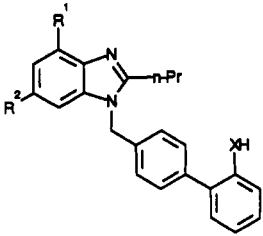
Scheme II[a]

20   R[1] = n-C$_5$H$_9$, R[2] = H

21   R[1], R[2] = -(CH$_2$)$_5$-

50a   R[1] = n-C$_5$H$_9$, R[2] = H

50b   R[1], R[2] = -(CH$_2$)$_5$-

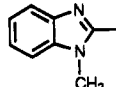[a](a) NaH, DMF; (b) R[1]R[2]NH, diglyme, 130 °C, 20 h; (c) H$_2$, Ra-Ni, AcOH; (d) CF$_3$COOH, CH$_2$Cl$_2$.
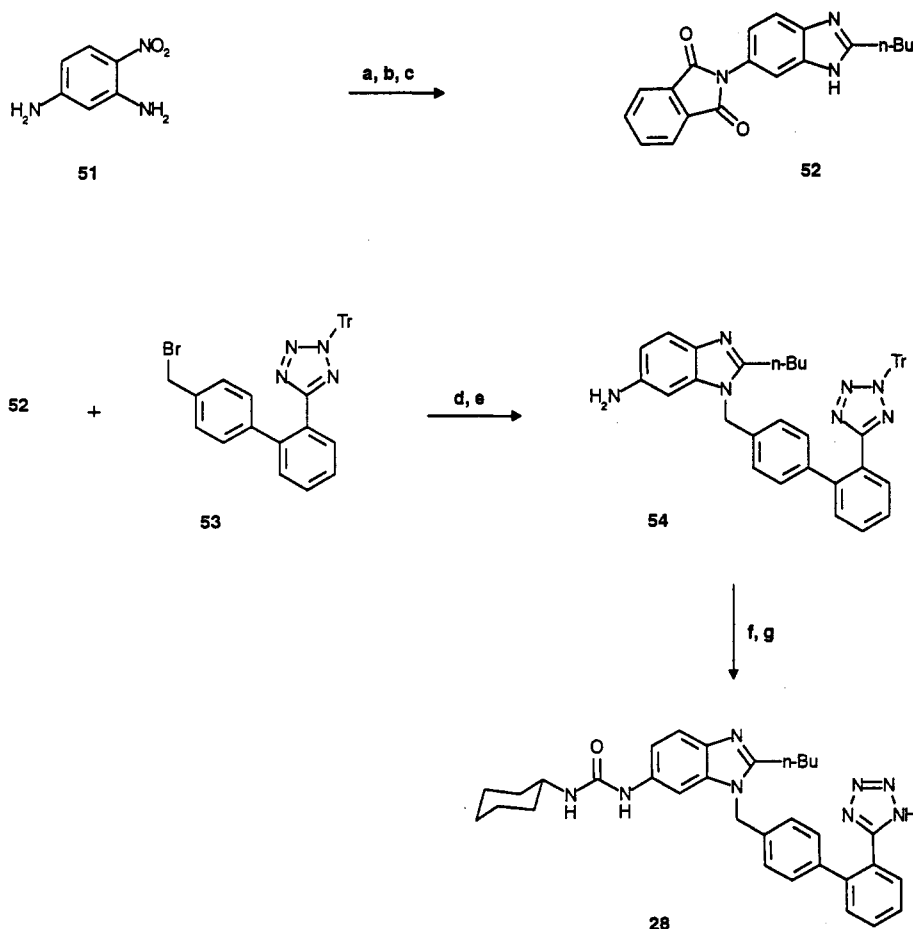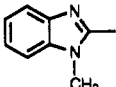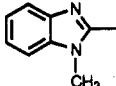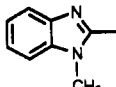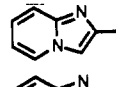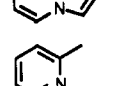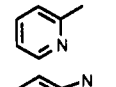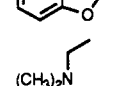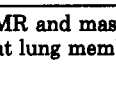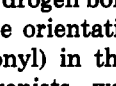
Scheme III[a]

[a](a) Phthalic anhydride, AcOH, reflux 2 h; (b) n-BuCOCl, C$_6$H$_5$Cl, 3 h, reflux; (c) H$_2$ (5 bar), Ra-Ni, 80 °C, AcOH; (d) KOt-Bu, DMSO; (e) CH$_3$NH$_2$, EtOH/DMF, chromatographic separation; (f) C$_6$H$_{11}$NCO, NEt$_3$, THF; (g) HCl, EtOH/CH$_2$Cl$_2$.

carbonyl oxygen of the carboxamide group which functions as a hydrogen acceptor. This hypothesis is supported by the fact that the *N*-methylurea **24** shows high affinity at the receptor, which demonstrates that the amide protons of **18, 22,** and **23** do not contribute to receptor binding. The interpretation is further supported by the potent receptor blockade of the *N-methylsulfonamide* **25.** In this case presumably one of the oxygen atoms of the

Table III. Effects of Benzimidazoles Substituted with Nitrogen-Containing Heterocycles in Position 6

| compd	R^1	R^2	XH	mp, °C	formula^a	IC$_{50}$, nM^b
33	CH$_3$		COOH	261–263	C$_{33}$H$_{33}$N$_4$O$_2$	3
34	H		COOH	217–218	C$_{32}$H$_{28}$N$_4$O$_2$	3
35	CH$_3$		tetrazole	228–230	C$_{33}$H$_{30}$N$_8$	13
36	H		tetrazole	198–200	C$_{32}$H$_{28}$N$_8$	5
37	CH$_3$		COOH	299–303	C$_{32}$H$_{28}$N$_4$O$_2$	4
38	CH$_3$		tetrazole	>181 dec	C$_{32}$H$_{28}$N$_8$	3
39	CH$_3$		tetrazole	>136 dec	C$_{30}$H$_{27}$N$_7$·0.5H$_2$O	5
40	H		tetrazole	227–229 dec	C$_{29}$H$_{25}$N$_7$·0.5H$_2$O	11
41	H		tetrazole	235–238	C$_{31}$H$_{25}$N$_7$O	240
42	CH$_3$		COOH	114–115	C$_{28}$H$_{31}$N$_3$O$_2$·H$_2$O	158

^{a} All compounds exhibited NMR and mass spectra consistent with structure and gave satisfactory analyses C, H, N (±0.4%). ^{b} IC$_{50}$ for specific binding of [^{125}I]AII to rat lung membrane preparation. For details see the Experimental Section.

sulfonyl group is part of a hydrogen bond. In order to get some information about the orientation of the dipolar groups (carbonyl and sulfonyl) in the receptor bound conformation of the antagonists, we synthesized the conformationally more restricted cyclic amides **26** and **27**. Both compounds showed receptor affinities in the same range as the open-chain analogs **25** and **22**. We therefore concluded that orientations of the dipolar groups in the cyclic amides are similar to those of the open-chain analogs.

Variation of the acidic moiety in the DuPont compounds led to the result that the tetrazole derivatives (e.g. **1**) are much more active than the corresponding carboxylic acids (e.g. **2**).[19] In our series of benzimidazole derivatives these acidic groups showed different effects on receptor binding, depending on the substituents at the benzimidazole moiety. In the case of urea-substituted benzimidazoles, the change from carboxylic acid derivatives **18**, **23**, and **24** to the analoguos tetrazoles **28**, **29**, and **30** improved activity only slightly. In contrast to this finding, the lactam and sultam substituents in combination with the tetrazole moiety resulted in a significant increase in receptor affinity: 11-fold for the sultam **31** and 20-fold in the case of the lactam **32**.

Compounds **22–32** (Table II) were tested for AII antagonism in normotensive rats. After intravenous administration they exhibited strong inhibition of the AII pressor response, corresponding to their in vitro activity. However, in most cases the duration of action was disappointing: especially the carboxylic acid derivatives **22–27** were only short acting, but also with the tetrazole compounds **28–30** a considerable decrease in activity was observed 2 h after application. Only the sultam **31** and the lactam **32** exhibited more than 60% inhibition of the AII pressor response 2 h after iv administration of 0.3 mg/kg. We have no detailed information about the pharmacokinetic properties of these substances, but we assume that their excretion rate rather than metabolic inactivation might limit their duration of action.

Unfortunately, both **31** and **32** were only weakly active when given orally to conscious rats, possibly due to their extremely poor water solubility in the neutral and weakly acidic pH range. We therefore focused our synthetic work on additional variations of substituents in position 6 of the benzimidazole moiety. According to our binding model such substituents should be able to function as hydrogen acceptors. Our working hypothesis was fully confirmed

Scheme IV[a]

31 X = SO$_2$
32 X = CO
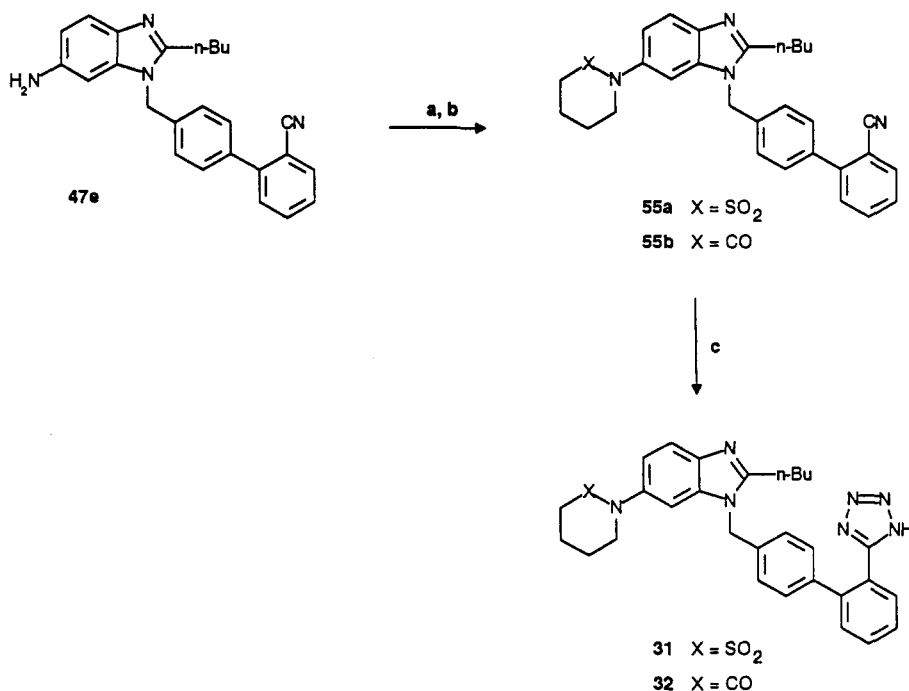
[a](a) Cl(CH$_2$)$_4$X Cl, NEt$_3$, THF; (b) NaOEt, EtOH; (c) NaN$_3$, NH$_4$Cl, DMF.
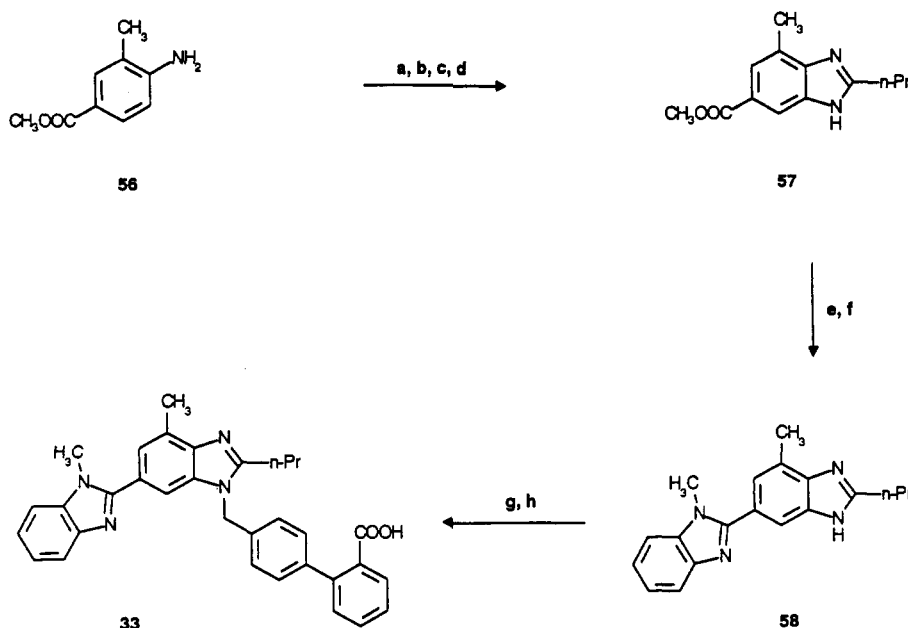
Scheme V[a]

[a](a) n-PrCOCl, C$_6$H$_5$Cl; (b) HNO$_3$, H$_2$SO$_4$; (c) H$_2$, Pd/C, MeOH; (d) AcOH; (e) NaOH, MeOH; (f) N-methyl-o-phenylenediamine, PPA, 150 °C; (g) 45, KOt-Bu, DMF; (h) CF$_3$COOH, CH$_2$Cl$_2$.

by the high receptor affinity of compounds substituted with nitrogen bearing heterocycles as hydrogen bond acceptors. As shown in Table III, substitution with an additional benzimidazole (compounds 33–36), an imidazopyridine (compounds 37 and 38), or a pyridine (compounds 39 and 40) led to highly active antagonists with IC$_{50}$ values in the low nanomolar range.

The most important common feature of these different heteroaromatic rings is a relatively high electron density at their nitrogen atom. In the case of the benzoxazole derivative 41, where the electron density at the nitrogen is much lower, we found a 48-fold lower receptor affinity compared to the isosteric benzimidazole 36. Also in accordance with our hypothesis is the finding that substitution with an aliphatic amine like in 42 leads to a

substantial drop in activity. Since the aminomethyl substituent is protonated under physiological conditions, it is no longer able to function as a hydrogen acceptor.

In our series of compounds the n-propyl residue in position 2 of the benzimidazole gave slightly higher affinities than the n-butyl group, as was also observed with a series of imidazole-type AII antagonists.[5c] The methyl group in position 4 (R^1 in Table III) has only a marginal effect on receptor affinity. It was introduced into the molecules for synthetic reasons in order to avoid isomeric mixtures in the alkylation reaction (step g in Scheme V).

Compounds 33–40 are highly active AII antagonists not only in vitro but also in vivo. Especially 33 (BIBR 277) turned out to be a very potent and long-acting antagonist

Scheme VI[a]
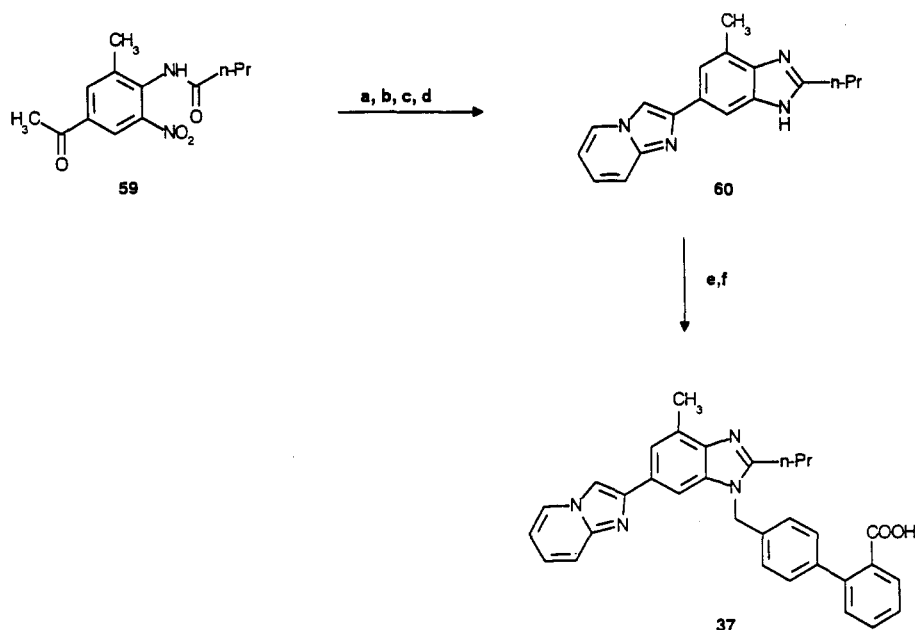
[a] (a) Dioxane–Br2, (C2H5)2O; (b) 2-aminopyridine, NEt3, EtOH; (c) Ra-Ni, N2H4, MeOH; (d) AcOH; (e) 45, KOt-Bu, DMF; (f) CF3COOH, CH2Cl2.

Scheme VII[a]
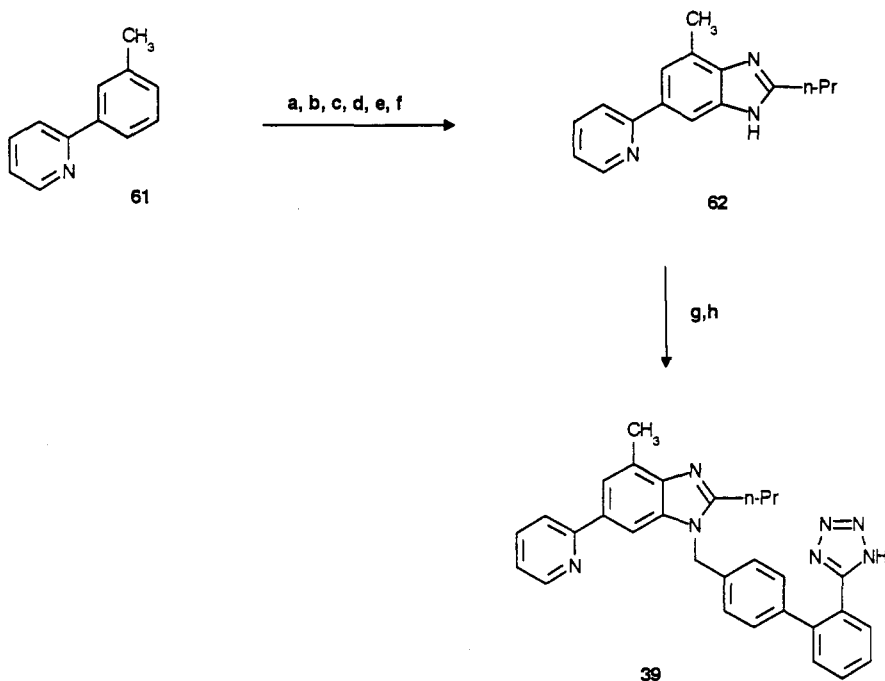
[a] (a) HNO3, –40 to 20 °C; (b) H2, Pd/C; (c) n-PrCOCl, C6H5Cl; (d) HNO3, H2SO4; (e) H2, Pd/C, MeOH; (f) AcOH; (g) 53, KOt-Bu, DMF; (h) HCl, EtOH.

after oral administration in rats. Because of its high potency and favorable pharmacokinetic behavior, **33** was chosen as a candidate for further pharmacological investigations.

Putative Binding Mode of Benzimidazole AII Antagonists. In order to obtain a better understanding of our experimental findings and to support our efforts to optimize biological activity, low-energy conformations of our test compounds were investigated by computer modeling techniques. Conformational analyses[22] of a large number of the benzimidazole-type angiotensin antagonists[12] resulted in a consistent 3D picture of their putative receptor bound conformations which is capable of explaining the observed structure-affinity relationships.

According to this model five pharmacophoric groups in our highly active inhibitors are important for receptor binding. This is illustrated in Figure 1 with **33** as an example. The position of the electron lone pair of the imidazole nitrogen atom was chosen as origin in Figure 1. Three other groups (a small alkyl residue (2), an acidic function (3), and a lipophilic aromatic group (4)) must be positioned in the magenta, red, and green areas, respectively. The fifth area shows the putative position of the hydrogen atom of an H-donor at the receptor. A strong interaction with this hydrogen atom is possible for the heteroatoms (N or O) of the position 6-substituents of the benzimidazole (Tables II and III).

Recently it has been shown that benzimidazole deriv-

| pharmacophore	function/interaction	group of AII inhibitor
1	hydrogen acceptor	lone pair of N-atom in benzimidazole
2	lipophilic vdW [α]	*n*-bu, *n*-pr side chain in 2-position
3	ionic	carboxylate, tetrazole attached to biphenyl
4	lipophilic aromatic	phenyl ring bearing group Nr 3
5	hydrogen acceptor	heteroatom of substituents in 6-position

[α] van der Waals interaction
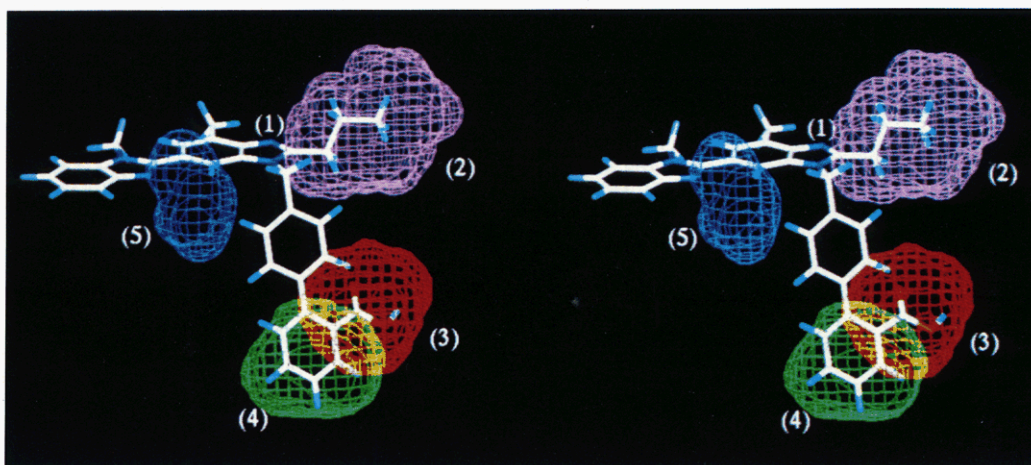
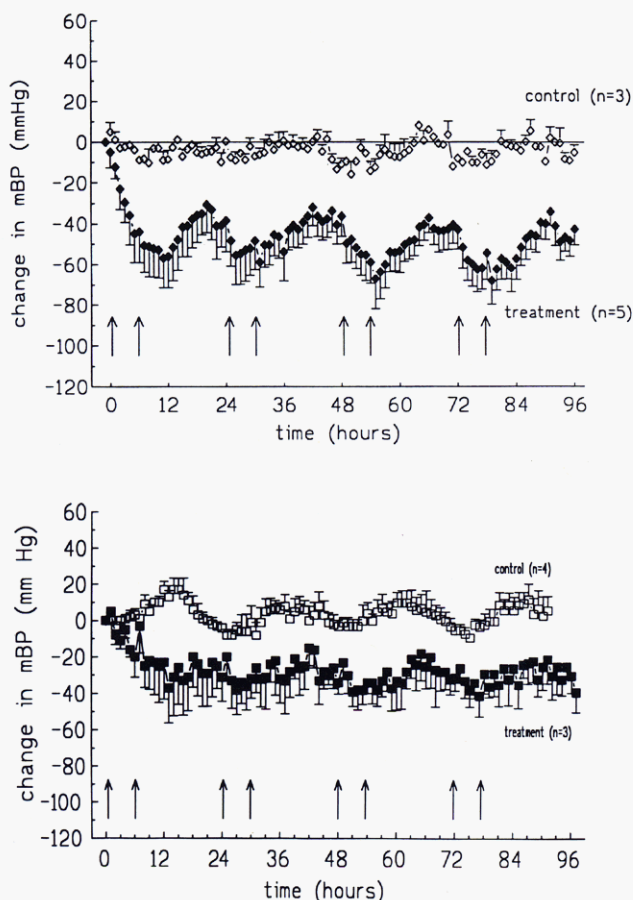**Figure 1.** Five pharmacophoric groups of benzimidazole AII inhibitors.

Figure 2. Effect of oral administration of (a) **33** (BIBR 277) (1.0 mg/kg bid) and (b) losartan (3 mg/kg bid) on mean arterial blood pressure of renovascular hypertensive, chronically instrumented, conscious rats during a 96-h treatment period. Results are presented as the mean ± SE of continuous measurements at 1-h intervals. Time points of administrations are indicated by arrows.

atives substituted with a carboxyl group in position 7 are also potent AII receptor antagonists.[23] Introduction of nitrogen atoms into the benzimidazole ring system in position 6 or 7 or substitution of the resulting imidazopyridines or imidazopyridazines with a carbonyl group also led to the identification of AII antagonists with improved activity compared to the unsubstituted benzimidazole derivatives.[24] According to our binding model the heteroatoms of these groups should be able to form a hydrogen bond with the AII receptor and function as a hydrogen acceptor.

Angiotensin II Antagonism in Vivo. Compound **33** was evaluated for its hypotensive activity in conscious chronically-instrumented renovascular hypertensive rats. These rats, which are characterized by an activated renin–angiotensin system, were instrumented with a chronic-use pressure transmitter in order to monitor blood pressure and heart rate. At a dosage of 1.0 mg/kg po bid for 4 days the fall in mean arterial blood pressure was 42 mmHg after the first treatment, from a starting value of 200 ± 3 mmHg, and reached a maximum fall of 68 mmHg after 4 days of treatment (Figure 2a). There were no significant changes in heart rate. For comparison, losartan in this hypertensive model elicited a lower antihypertensive activity at 3 mg/kg po bid (Figure 2b). From these data it was concluded that **33** in this model is approximately 3 times more potent than losartan. A more detailed description of the effects of **33** in vitro and in vivo has been published recently.[25]

On the basis of these results **33** (BIBR 277) has been selected for development and is currently undergoing clinical trials.

Conclusion

With DuP 753 (losartan) as a lead structure, new angiotensin II antagonists were explored employing a benzimidazole instead of the substituted imidazole ring as the main skeleton. The influence of a variety of benzimidazole substituents on receptor binding was examined. Structure–activity relationships, supported by

conformational analyses and molecular modeling, revealed that especially the substituents which strongly increase affinity contribute to receptor binding via an additional hydrogen bond. On the basis of this knowledge a number of highly active antagonists were designed from which **33** (BIBR 277) was selected for development because of its favorable pharmacokinetic behavior. This compound is currently undergoing clinical trials in hypertensive patients.

Experimental Section

(a) Chemistry. Melting points were determined in a Buchi capillary melting point apparatus and were uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer Model 298 spectrophotometer. ^{1}H-NMR spectra were measured on a Bruker AC200 and a Bruker AMX400 instrument. Chemical shifts are reported in δ units relative to internal tetramethylsilane. Mass spectra were recorded on a Finnigan MAT 8230 or a AEI MS-902 mass spectrometer in either EI or fast-atom-bombardment mode. Microanalyses were performed on a CHN-Rapid (Heraeus). Silica gel (Baker 30–60 μm) was used for column chromatography. TLC was performed on silica gel plates (Macherey-Nagel Polygram Sil G/UV 254 or Merck, silica gel 60, F-254).

2-n-Butyl-5-nitrobenzimidazole (44b). A solution of 11.5 g (75 mmol) of 1,2-diamino-4-nitrobenzene and 8.66 g (85 mmol) of valeric acid in 120 mL of POCl$_3$ was heated under reflux for 3 h. The mixture was then poured on 1.5 L of ice water, the pH was adjusted to 8–10 by addition of concentrated ammonia, and the solution was extracted with ethyl acetate. The extracts were dried, the solvent was evaporated, and the residue was purified by silica gel column chromatography, eluting with dichloromethane/ethanol (98:2 v/v) to give **44b** (10.2 g, 62%) as brown solid: mp 139–141 °C; ^{1}H-NMR (CDCl$_3$) δ 1.0 (t, 3H), 1.5 (m, 2H), 1.9 (m, 2H), 3.0 (t, 2H), 7.6 (d, 1H), 8.2 (dd, 1H), 8.5 (s, 1H), 9.5–10.5 (br, 1H). Anal. (C$_{11}$H$_{13}$N$_3$O$_2$) C, H, N.

2-n-Butyl-4-nitrobenzimidazole (44a). The title compound was prepared from 1,2-diamino-3-nitrobenzene by the same as procedure described for the preparation of **44b**: 98% yield; mp 171–173 °C; ^{1}H-NMR (d_6-DMSO) δ 0.9 (t, 3H), 1.4 (m, 2H), 1.8 (m, 2H), 2.9 (t, 2H), 7.4 (t, 1H), 8.1 (dd, 2H). Anal. (C$_{11}$H$_{13}$N$_3$O$_2$) C, H, N.

Mixture of $tert$-Butyl 4′-[(2-n-Butyl-5/6-nitrobenzimidazol-1-yl)methyl]biphenyl-2-carboxylate (46b). To a solution of 9.5 g (43 mmol) of 2-n-butyl-5-nitrobenzimidazole (**44b**) in 100 mL of DMSO was added potassium $tert$-butylate (5.3 g, 47.6 mmol), the mixture was stirred for 30 min at ambient temperature, and $tert$-butyl 4′-(bromomethyl)biphenyl-2-carboxylate (**45**) (16.6 g, 47.6 mmol) was added. After stirring for 14 h the mixture was poured into water (400 mL) and extracted with ethyl acetate (3 × 100 mL). The combined extracts were dried (MgSO$_4$) and evaporated. The residue was purified by silica gel column chromatography eluting with dichloromethane/ethanol (99:1 v/v) to give **46b** (19.9 g, 95%) as an oil: ^{1}H-NMR (CDCl$_3$) δ 1.0 (t, 3H), 1.2 (d, 9H), 1.5 (m, 2H), 1.4 (m, 2H), 3.0 (m, 2H), 5.5 (d, 2H), 7.1 (d, 2H), 7.2–7.5 (m, 4H), 7.8 (m, 2H), 8.2 (m, 2H), 8.7 (d, 1H). Anal. (C$_{29}$H$_{31}$N$_3$O$_4$) C, H, N.

Mixture of $tert$-Butyl 4′-[(2-n-Butyl-4/7-nitrobenzimidazol-1-yl)methyl]biphenyl-2-carboxylate (46a). The title compound was prepared from 2-n-butyl-4-nitrobenzimidazole (**44a**) by the same procedure as described for the preparation of **46b**: 97% yield; ^{1}H-NMR (CDCl$_3$) δ 0.9 (t, 3H), 1.2 (s, 9H), 1.5 (m, 2H), 1.9 (m, 2H), 3.0 (t, 2H), 5.5 (s, 2H), 7.0 (d, 2H), 7.2–7.5 (m, 7H), 7.8 (d, 1H), 8.1 (d, 1H). Anal. (C$_{29}$H$_{31}$N$_3$O$_4$) C, H, N.

$tert$-Butyl 4′-[(2-n-Butyl-5-aminobenzimidazol-1-yl)methyl]biphenyl-2-carboxylate (47b) and $tert$-Butyl 4′-[(2-n-Butyl-6-aminobenzimidazol-1-yl)methyl]biphenyl-2-carboxylate (47c). The mixture of isomeric nitro compounds (**46b**) (13.8 g, 28.5 mmol) was reduced in ethanol (200 mL) with Raney nickel (10 g) and hydrogen (5 bar) at 50 °C. After filtration the solvent was evaporated in vacuo. Purification and separation of the isomeric compounds by silica gel column chromatography (eluant: dichloromethane/ethanol 50:1 and 25:1 v/v) gave **47b** (oil, 6.9 g, 53%, R_f 0.1 (dichloromethane/ethanol, 19:1)) and **47c** (oil, 5.4 g, 42%, R_f 0.2 (dichloromethane/ethanol, 19:1)). **47b**: ^{1}H-NMR (CDCl$_3$) δ 0.9 (t, 3H), 1.3 (s, 9H), 1.5 (m, 2H), 1.8 (m,

2H), 2.8 (t, 2H), 3.5 (br, 2H), 5.3 (s, 2H), 6.6 (dd, 1H), 7.0–7.5 (m, 9H), 7.8 (d, 1H). **47c**: ^{1}H-NMR (CDCl$_3$) δ 0.9 (t, 3H), 1.3 (s, 9H), 1.5 (m, 2H), 1.8 (m, 2H), 2.8 (t, 2H), 3.6 (br, 2H), 5.3 (s, 2H), 6.5 (d, 1H), 6.6 (d, 1H), 7.0–7.5 (m, 8H), 7.8 (d, 1H).

$tert$-Butyl 4′-[(2-n-Butyl-4-aminobenzimidazol-1-yl)methyl]biphenyl-2-carboxylate (47a) and $tert$-Butyl 4′-[(2-n-Butyl-7-aminobenzimidazol-1-yl)methyl]biphenyl-2-carboxylate (47d). The title compounds were prepared from $tert$-butyl 4′-[(2-n-butyl-4/7-nitrobenzimidazol-1-yl)methyl]biphenyl-2-carboxylate (**46a**) by the same procedure described for the preparation of 47b and 47c. **47a**: mp 89–91 °C; 86% yield; R_f 0.2 (dichloromethane/ethanol, 99:1); ^{1}H-NMR (CDCl$_3$) δ 0.9 (t, 3H), 1.3 (s, 9H), 1.5 (m, 2H), 1.9 (m, 2H), 2.8 (t, 2H), 3.4 (br, 2H), 5.7 (s, 2H), 6.5 (s, 1H), 7.0–7.5 (9H), 7.8 (d, 1H). **47d**: oil; 5% yield; R_f 0.2 (dichloromethane/ethanol, 99:1), ^{1}H-NMR (CDCl$_3$) δ 0.9 (t, 3H), 1.2 (s, 9H), 1.5 (m, 2H), 1.8 (m, 2H), 2.9 (t, 2H), 4.4 (br, 2H), 5.3 (s, 2H), 6.5 (d, 1H), 6.6 (d, 1H), 7.0–7.5 (m, 8H), 7.8 (d, 1H).

4′-[(2-n-Butyl-6-aminobenzimidazol-1-yl)methyl]biphenyl-2-carboxylic Acid (10). To a solution of 1.5 g (3.3 mmol) of 47c in 15 mL of dichloromethane was added trifluoroacetic acid (15 mL). After stirring for 24 h at 25 °C the mixture was evaporated in vacuo, dissolved in dichloromethane (100 mL), and extracted with water (3 × 50 mL). The combined aqueous phases were evaporated in vacuo, dissolved in dichloromethane, and dried (MgSO$_4$). The solvent was removed, and the residue was dried to give **10** (1.5 g, 73%) as a solid: mp 72–74 °C; ^{1}H-NMR (d_6-DMSO) δ 0.9 (t, 3H), 1.4 (m, 2H), 1.7 (m, 2H), 3.2 (t, 2H), 5.7 (s, 2H), 6.9 (m, 2H), 7.2–7.6 (m, 8H), 7.7 (d, 1H). Anal. (C$_{25}$H$_{25}$N$_3$O$_2$·2CF$_3$COOH) C, H, N.

4′-[(2-n-Butyl-6-acetamidobenzimidazol-1-yl)methyl]biphenyl-2-carboxylic Acid (14). To a solution of 1.2 g (2.6 mmol) of 47c in 15 mL of pyridine was added at 0 °C acetyl chloride (0.5 mL). After stirring for 1 h at 25 °C the mixture was poured on ice water (50 mL). The precipitated solid was filtered off, dried, and dissolved in dichloromethane (25 mL). After addition of trifluoroacetic acid (10 mL) the mixture was stirred for 24 h at ambient temperature and then evaporated in vacuo and dissolved in water (100 mL). The pH was adjusted to 8 by addition of concentrated ammonia, and the solution was filtered and acidified by addition of acetic acid. The precipitated solid was filtered off and dried to give **14** (0.87 g, 87%) as a white solid: mp 252–254 °C; ^{1}H-NMR (d_6-DMSO) δ 0.9 (t, 3H), 1.4 (m, 2H), 1.7 (m, 2H), 2.0 (s, 3H), 2.8 (t, 2H), 5.4 (s, 2H), 7.1–7.9 (m, 11H). Anal. (C$_{27}$H$_{27}$N$_3$O$_3$) C, H, N.

4′-[[2-n-Butyl-6-[[(cyclohexylamino)carbonyl]amino]-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic Acid (18). To a solution of 1.5 g (3.3 mmol) of 47c in 40 mL of THF was added 2.0 g (20 mmol) of triethylamine and 1.53 g (12 mmol) of cyclohexyl isocyanate. The mixture was heated under reflux for 5 h and evaporated in vacuo. The residue was purified by silica gel column chromatography, eluting with dichloromethane/ethanol (98:2 v/v). The pure $tert$-butyl ester was transformed into the analogous carboxylic acid by the same procedure as described for the preparation of 14 to give **18** (1.6 g, 76%) as a white solid: mp 199–200 °C; ^{1}H-NMR (d_6-DMSO) δ 0.9 (t, 3H), 1.1–1.9 (m, 14H), 3.1 (t, 2H), 3.5 (br, 1H), 5.6 (s, 2H), 6.2 (d, 1H), 7.2– 7.8 (m, 10H), 8.0 (d, 1H), 8.7 (s, 1H), 12.7 (br, 1H). Anal. (C$_{32}$H$_{36}$N$_4$O$_3$·CF$_3$COOH) C, H, N.

4′-[[2-n-Butyl-4-[[(cyclohexylamino)carbonyl]amino]-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic Acid (16). The title compound was prepared from 47a by the same procedure as described for the preparation of 18: mp 242–244 °C dec; 94% yield; ^{1}H-NMR (d_6-DMSO) δ 0.9 (t, 3H), 1.1–1.9 (m, 14H), 2.9 (t, 2H), 3.5 (br, 1H), 5.5 (s, 2H), 7.0–7.9 (m, 12H), 8.4 (s, 1H), 12.7 (s, 1H). Anal. (C$_{32}$H$_{36}$N$_4$O$_3$) C, H, N.

N-[2-Nitro-5-(n-pentylamino)phenyl]-N-valeroyl[2′-($tert$-butoxycarbonyl)biphenyl-4-yl]methylamine (50a). To a solution of 2.6 g (5.0 mmol) 49 in 15 mL diethylene glycol dimethyl ether was added 13.3 g (0.15 mol) of n-pentylamine. In a sealed tube the mixture was heated to 150 °C for 28 h. After evaporation the residue was dissolved in ethyl acetate (200 mL) and the solution was extracted with water (100 mL). The organic layer was dried (MgSO$_4$) and the solvent was evaporated. The residue was purified by silica gel column chromatography eluting with dichloromethane/ethanol (99:1 v/v) to give **50a** (2.2 g, 77%) as a light yellow oil: ^{1}H-NMR (CDCl$_3$) δ 0.8–0.9 (m, 6H), 1.2–1.4

(m, 16H), 1.5–1.7 (m, 4H), 2.1 (t, 2H), 3.0 (m, 2H), 3.9 (d, 1H), 4.8 (t, 1H), 5.1 (d, 1H), 5.3 (d, 1H), 6.5 (dd, 1H), 7.5–7.8 (m, 7H), 8.1 (d, 1H).

4′-[[2-n-Butyl-6-(n-pentylamino)benzimidazol-1-yl]methyl]biphenyl-2-carboxylic Acid (20). 50a (2.2 g, 3.8 mmol) in 50 mL methanol was reduced with Raney nickel (0.2 g) and hydrogen (5 bar) at 25 °C. After filtration the solvent was evaporated, and the residue was dissolved in glacial acetic acid (20 mL) and heated under reflux for 1 h. After evaporation in vacuo, water (50 mL) was added, the pH was adjusted to 8 by addition of concentrated ammonia, and the mixture was extracted with ethyl acetate (3 × 50 mL). The combined extracts were dried, the solvent was evaporated, and the residue was dried. The pure *tert*-butyl ester was transformed into the analogous carboxylic acid by the same procedure as described for the preparation of 14 to give 20 (1.2 g, 67%) as a light yellow solid: mp 108–113 °C; ¹H-NMR (CDCl₃) δ 0.9 (m, 6H), 1.3–1.8 (m, 10H), 2.8 (t, 2H), 3.1 (t, 2H), 5.3 (s, 2H), 6.3 (s, 1H), 6.4 (d, 1H), 6.6 (dd, 1H), 7.1 (d, 2H), 7.2–7.6 (m, 7H). Anal. (C₃₀H₃₅N₃O₂) C, H, N.

4′-[(2-n-Butyl-6-amino-benzimidazol-1-yl)methyl]-2-[2-(triphenylmethyl)tetrazol-5-yl]biphenyl (54). To a solution of 9.4 g (29.4 mmol) of 2-n-butyl-5-phthalimidobenzimidazole (52) in 100 mL of DMSO were added 3.6 g (32.2 mmol) of potassium *tert*-butylate and, after 1 h, 18.3 g of 4′-(bromomethyl)-2-[2-(triphenylmethyl)tetrazol-5-yl]biphenyl (53). Reaction and workup were performed by the same procedure as described for the preparation of 46b. The resulting mixture of the isomeric phthalimides (14.0 g) was dissolved in ethanol (150 mL) and DMF (30 mL), and aqueous methylamine (40%, 20 mL) was added. The solution was stirred at ambient temperature for 4 h, the solvent was evaporated, and the residue was dissolved in acetone (150 mL). After filtration and evaporation in vacuo the residue was purified by silica gel column chromatography eluting with dichloromethane/ethanol (200:1, 100:1, and 50:1 v/v) to give 54 (4.4 g, 22%) as a colorless foam: ¹H-NMR (CDCl₃) δ 0.9 (t, 3H), 1.2–1.5 (m, 2H), 1.7–1.9 (m, 2H), 2.7 (t, 2H), 3.4 (br, 2H), 5.1 (s, 2H), 6.3 (d, 1H), 6.6 (dd, 1H), 6.8–7.5 (m, 23H), 7.9 (dd, 1H). Anal. (C₄₄H₄₂N₇) C, H, N.

4′-[[2-n-Butyl-6-[[(cyclohexylamino)carbonyl]amino]-benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)biphenyl (28). A 1.0-g (1.5-mmol) portion of 54 was transformed into the analogous cyclohexylurea by addition of cyclohexyl isocyanate and triethylamine by the same procedure as described for the preparation of 18. The crude urea (0.84 g) was dissolved in 60 mL of dichloromethane/ethanol (1:1 v/v), ethanolic HCl (10 ml) was added, and the solution was stirred at ambient temperature for 18 h. The solvent was evaporated, and concentrated ammonia was added to the residue. After filtration the residue was purified by silica gel column chromatography eluting with ethyl acetate/ethanol/ammonia (95:5 : 0.05 and 80:20 :0.05 v/v) to give 28 (0.32 g, 39%) as a white solid: mp 232–234 °C; ¹H-NMR (d₆-DMSO) δ 0.9 (t, 3H), 1.0–1.9 (m, 15H), 2.8 (t, 2H), 3.5 (m, 1H), 5.4 (s, 2H), 6.0 (d, 1H), 6.9–7.1 (m, 5H), 7.4–7.7 (m, 6H), 8.3 (s, 1H). Anal. (C₃₂H₃₆N₈O) C, H, N.

4′-[[2-n-Butyl-6-(butanesultam-1-yl)benzimidazol-1-yl]-methyl]-2-cyanobiphenyl (55a). To a solution of 1.0 g (2.6 mmol) of 4′-[(2-n-butyl-6-aminobenzimidazol-1-yl)methyl]-2-cyanobiphenyl 47e, prepared in a similar manner as described for the preparation of 47c, in THF (50 mL) were added 4-chloro-1-butanesulfonyl chloride (0.5 g, 2.6 mmol) and triethylamine (1 ml, 3.0 mmol), and the mixture was stirred for 5 h at ambient temperature. After filtration the solvent was evaporated, and the residue was dissolved in a solution of sodium ethylate (2.95 g, 43 mmol) in ethanol (100 mL). The mixture was heated under reflux for 1 h, then the solvent was evaporated, and the residue was purified by silica gel column chromatography, eluting with dichloromethane/ethanol (19:1 v/v) to give 55a (0.64 g, 50%) as a white solid: mp 158–160 °C; ¹H-NMR (CDCl₃) δ 0.9 (t, 3H), 1.4 (m, 2H), 1.8 m, 2H), 2.0 (m, 2H), 2.4 (m, 2H), 2.8 (t, 2H), 3.3 (t, 2H), 3.7 (t, 2H), 5.5 (s, 2H), 7.1–7.3 (m, 4H), 7.4–7.8 (m, 7H).

4′-[[2-n-Butyl-6-(2-oxopiperidin-1-yl)benzimidazol-1-yl]-methyl]-2-cyanobiphenyl (55b). The title compound was prepared from 47e and 4-chlorovaleroyl chloride by the same procedure as described for the preparation of 55a: 80% yield; mp 180–182 °C; ¹H-NMR (CDCl₃) δ 0.9 (t, 3H), 1.4 (m, 2H),

1.8–2.0 (m, 6H), 2.5 (m, 2H), 2.9 (t, 2H), 3.7 (m, 2H), 5.4 (s, 2H), 7.1–7.2 (m, 4H), 7.4–7.8 (m, 7H).

4′-[[2-n-Butyl-6-(butanesultam-1-yl)benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)biphenyl (31). To a solution of 0.64 g (1.3 mmol) of 55a in DMF (20 mL) were added sodium azide (845 mg, 1.3 mmol) and ammonium chloride (693 mg, 1.3 mmol), and the mixture was heated at 140 °C for 18 h. After cooling, water (50 mL) was added, and the precipitated solid was filtered off, dried, and purified by silica gel column chromatography eluting with dichloromethane/ethanol (99:1 and 93:7 v/v) to give 31 (0.22 g, 31%) as a white solid: mp 189–191 °C; ¹H-NMR (CDCl₃) δ 0.9 (t, 3H), 1.4 (m, 2H), 1.8 (m, 2H), 2.0 (m, 2H), 2.4 (m, 2H), 2.8 (t, 2H), 3.3 (t, 2H), 3.7 (t, 2H), 5.4 (s, 2H), 6.8–7.1 (m, 6H), 7.4–7.6 (m, 4H), 7.9 (dd, 1H). Anal. (C₂₉H₃₁N₇O₂S) C, H, N.

4′-[[2-n-Butyl-6-(2-oxopiperidin-1-yl)benzimidazol-1-yl]-methyl]-2-(1H-tetrazol-5-yl)biphenyl (32). The title compound was prepared from 55b by the same procedure as described for the preparation of 31: 50% yield; mp 163–165 °C; ¹H-NMR (CDCl₃) δ 0.9 (t, 3H), 1.4 (m, 2H), 1.7–2.1 (m, 6H), 2.6 (7, 2H), 2.9 (t, 2H), 3.7 (m, 2H), 5.3 (s, 2H), 6.8 (d, 2H), 7.0 (m, 4H), 7.4–7.7 (m, 4H), 7.9 (dd, 1H). Anal. (C₃₀H₃₁N₇O) C, H, N.

2-n-Propyl-4-methyl-6-(methoxycarbonyl)benzimida-zole (57). Methyl 4-amino-3-methylbenzoate (56) (8.25 g, 50 mmol) was acylated with butyryl chloride (5.3 mL, 50 mmol) in chlorobenzene at 100 °C. The resulting amide was reacted with fuming nitric acid in sulfuric acid (60%) at 0 °C. The resulting methyl 4-(butyrylamino)-3-methyl-5-nitrobenzoate was reduced with hydrogen (5 bar) and palladium (10% on carbon) in methanol by the same procedure as described for the preparation of 47b/47c. The resulting amino compound was dissolved in glacial acetic acid and heated under reflux for 1.5 h. After evaporation of the acetic acid water was added and the pH was adjusted to 9 by addition of concentrated ammonia. This solution was extracted with ethyl acetate (3 × 100 mL), and the combined organic layers were washed with aqueous NaHCO₃ solution and dried (MgSO₄). After addition of charcoal and fitration the solvent was evaporated to give 57 (9.0 g, 78% overall) as an oil: ¹H-NMR (CDCl₃) δ 1.0 (t, 3H), 1.9 (m, 2H), 2.4 (s, 3H), 2.9 (t, 2H), 3.9 (s, 3H), 7.8 (2, 1H), 8.1 (s, 1H).

2-n-Propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)benz-imidazole (58). To a solution of 6.9 g (30 mmol) of 57 in methanol (500 mL) was added a solution of 40 g of NaOH in water (300 mL), and the mixture was heated under reflux for 2 h. After evaporation of methanol, water (700 mL) was added to the residue and the pH was adjusted to 5 by addition of aqueous citric acid (30%). The precipitated solid was washed with ethanol, filtered off, and dried to yield 5.46 g (25 mmol) of 2-n-propyl-4-methyl-6-carboxybenzimidazole. This was dissolved in polyphosphoric acid (65 g) at 150 °C, and N-methyl-o-phenylenediamine dihydrochloride (4.88 g, 25 mmol) was added in small portions. After stirring at 150 °C for 20 h the mixture was allowed to cool and then poured into water (300 mL). The pH was adjusted to 9 by addition of concentrated ammonia (ice cooling). The precipitated solid was filtered off, dried, and boiled in ethyl acetate (300 mL). After cooling, the solid was filtered off, washed with diethyl ether, and dried to give 58 (5.86 g, 64% overall) as a white solid: mp 193–195 °C; ¹H-NMR (CDCl₃) δ 0.9 (t, 3H), 1.7 (m, 2H), 2.6 (s, 3H), 2.8 (t, 2H), 3.9 (2, 3H), 7.3–7.5 (m, 4H), 7.8 (d, 2H).

4′-[[2-n-Propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic Acid (33). The title compound was prepared from 58 and 45 by the same procedure decribed for the preparation of 46b. After chromatographic separation the *tert*-butyl ester was cleaved as described for the preparation of 14 to give 33 (42% yield overall) as a white solid: mp 261–263 °C; ¹H-NMR (d₆-DMSO) δ 1.0 (t, 3H), 1.8 (m, 2H), 2.6 (s, 3H), 2.9 (t, 2H), 3.8 (s, 3H), 5.6 (s, 2H), 7.1–7.8 (m, 14H). Anal. (C₃₃H₃₃N₄O₂) C, H, N.

2-n-Propyl-4-methyl-6-(imidazo[1,2-a]pyridin-2-yl)benz-imidazole (60). To a solution of 2.8 g (10.6 mmol) of 4-(n-butyrylamino)-3-methyl-5-nitroacetophenone (59) in 100 mL of diethyl ether at ambient temperature was added dropwise a solution of 0.55 mL of bromine in 15 mL of 1,4-dioxane. After 15 min the mixture was washed with water and NaHCO₃ solution (5%) and dried (Na₂SO₄) The solvent was evaporated, and the crude residue (3.53 g) was dissolved in ethanol (70 mL). After addition of 2-aminopyridine (0.94 g, 10.0 mmol) and triethylamine

(2 mL, 14.3 mmol), the solution was heated under reflux for 2 h. The solvent was evaporated, and the crude 2-(n-butyrylamino)-3-methyl-1,5-nitro-6-(imidazo[1,2-a]pyridin-2-yl)benzene was purified by silica gel column chromatography eluting with dichloromethane. The nitro group of this intermediate was reduced with hydrazine hydrate (80%, 2 mL) and Raney nickel (1 g) in boiling methanol (200 mL), and the resulting amino compound was heated in glacial acetic acid by the same procedure as described for the preparation of 57 to give 60 (0.85 g, 28% yield overall) as an oil: ¹H-NMR (d_6-DMSO) δ 1.0 (t, 3H), 1.9 (m, 2H), 2.5 (s, 3H), 2.9 (t, 2H), 6.9 (dd, 1H), 7.2 (dd, 1H), 7.6 (d, 2H), 7.9 (2, 1H), 8.3 (s, 1H), 8.5 (d, 1H).

4'-[[2-n-Propyl-4-methyl-6-(imidazo[1,2-a]pyridin-2-yl)-benzimidazol-1-yl]methyl]biphenyl-2-carboxylic Acid (37). The title compound was prepared from 60 and 45 by the same procedure decribed for the preparation of 46b. After chromatographic separation of the intermediate the tert-butyl ester was cleaved as described for the preparation of 14 to give 37 (51% yield overall) as a white solid: mp 299–303 °C; ¹H-NMR (d_6-DMSO) δ 1.0 (t, 3H), 1.8 (m, 2H), 2.6 (s, 3H), 2.9 (t, 2H), 5.6 (s, 2H), 6.9 (dd, 1H), 7.1–7.7 (m, 11H), 7.9 (s, 1H), 8.3 (s, 1H), 8.5 (d, 1H). Anal. ($C_{32}H_{28}N_4O_2$) C, H, N.

2-n-Propyl-4-methyl-6-(pyridin-2-yl)benzimidazole (62). To 3 mL of fuming nitric acid at −40 to −20 °C was added dropwise 2-(3-methylphenyl)pyridine (1.0 g, 5.6 mmol). After 30 min at −8 °C the mixture was poured on ice water and the precipitate was filtered off. It was then dissolved in water (50 ml), the pH was adjusted to 10 by addition of concentrated ammonia, and the precipitated solid was filtered off and dried. The thus obtained 2-(3-methyl-4-nitrophenyl)pyridine (0.6 g) was reduced with hydrogen and palladium (10% on carbon). Acylation of the resulting amino compound with butyryl chloride in chlorobenzene, nitration, hydrogenation, and formation of the benzimidazole were preformed by the same procedures as described for the preparation of 57 to give 62 (0.25 g, 17% yield overall) as an oil: ¹H-NMR (d_6-DMSO) δ 1.0 (t, 3H), 1.8 (m, 2H), 2.5 (s, 3H), 2.8 (t, 2H), 7.3 (m, 1H), 7.7–8.1 (m, 4H), 8.6 (m, 1H), 12.2 (s, 1H).

4'-[[2-n-Propyl-4-methyl-6-(pyridin-2-yl)benzimidazol-1-yl]methyl]-2-(1H-tetrazol-5-yl)biphenyl (39). To a solution of 0.25 g (1.0 mmol) of 62 in 3 mL of DMF were added 0.13 g (1.2 mmol) of potassium tert-butylate and, after 1 h, 0.67 g (1.2 mmol) of 53. Reaction and workup were performed by the same procedure described for the preparation of 46b. The resulting N-trityltetrazole derivative (0.45 g) was deprotected with ethanolic HCl by the same procedure as described for the preparation of 28 to give 39 (0.17 g, 35% yield overall) as a white solid: mp >136 °C dec; ¹H-NMR (CDCl₃) δ 0.9 (t, 3H), 1.7 (m, 2H), 2.5 (s, 3H), 2.6 (t, 2H), 5.3 (s, 2H), 6.7 (d, 2H), 6.9 (d, 2H), 7.2–7.8 (m, 9H), 8.5 (d, 1H), 11.0 (br, 1H). Anal. ($X_{30}H_{27}N_7$·0.5 H₂O) C, H, N.

Angiotensin Receptor Binding Studies. Membrane preparations from rat lung were obtained as follows. Male Wistar rats (strain Chbb:THOM, 200–220 g) were killed by a blow to the neck. The lung was dissected out, cleaned, and homogenized in Tris-buffer (50 mM Tris, 150 mM NaCl, 5 mM EDTA, pH 7.20) by use of an Ultra Turrax at maximal setting for 30 s. The homogenate was centrifuged for 10 min at 1000g, and the resulting supernatant was recentrifuged twice for 20 min at 48 000g. The final pellet was resuspended in incubation buffer (50 mM Tris, 5 mM MgCl₂, 0.2% bovine serum albumin, pH 7.20) before performing binding experiments in triplicate.

For competition experiments protein (40–100 μg) was incubated with 50 pM [¹²⁵I]AII New England Nuclear (Dreieich, Germany) and increasing concentrations of the competitor at 37 °C for 60 min in a total volume of 0.2 mL. The test compounds had been dissolved in water or dimethyl sulfoxide, if necessary, and diluted adequately. A maximal DMSO concentration of 1% (v/v) was used which was shown not to decrease specific binding of the radioligand. Test concentrations of the competitor were chosen to bracket the expected IC₅₀ (concentration for 50% displacement of the specifically bound [¹²⁵I]AII) and to cover at least 5 orders of magnitude. The incubations were terminated by rapid filtration through SF/B-glass fibre filters using a Scatron cell harvester. The filters were washed twice with ice-cold buffer, and particle-bound radioligand was assayed in a g-counter. Nonspecific binding was defined as radioactivity bound in the presence of excess (1 μM) AII in the incubation medium. Specific binding in the presence of the drug was compared to the control specific binding. IC₅₀ values were determined from the relationship between the specifically bound radioactivity and drug concentration using a least-square nonlinear curve fitting program (RS/1 software package (BBN Research Systems, Cambridge, MA)). Values were corrected for the radioligand occupancy shift to obtain the inhibition constant (K_i) according to Cheng and Prusoff.[26] Protein was determined according to the method of Lowry et al.[27] using bovine serum albumin as standard.

Under the assay conditions used, the total binding was typically in the range of 0.13–0.25 fmol/200 μL. Nonspecific binding did not exceed 15% of the total binding. The IC₅₀ for unlabeled AII in this assy was 1.88 + 0.17 nM (mean + SEM, n = 50). Intraassay and interassay IC₅₀ values for a given test compound vary less than 10% and less than 15%, respectively.

Effects on Blood Pressure in Renal Hypertensive Rats. Male rats (Chbb:THOM; 140–150 g) are anaesthetized with pentobarbitone–sodium (50 mg/kg ip). The abdominal cavity is opened by a midline incision. A solid silver clip with an internal diameter of 0.20 mm is applied to the left renal artery as close as possible to the aorta. Care is taken that the artery rests at the base of the slit and that a visible blood flow remains in the artery behind the clip. The contralateral kidney is not disturbed. The catheter of a pressure transmitter (TA11PA-C40) is inserted in the abdominal aorta and the transmitter is fixed to abdominal musculature. The abdomen is closed with Mersilene sutures. The animals are allowed to recover for several weeks and housed individually in Macrolon cages.

After the implantation of the chronic-use device, blood pressure and heart rate are transmitted by telemetry and the signals are received by a RA 1010 General Purpose Receiver (Data Sciences Inc) Data are acquired with the Dataquest IV 1.11 system on an Hewlett Packard Vectra ES/12 386 computer. Analysis of the data is performed by an in-house software package.

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