Nonpeptide Angiotensin II Receptor Antagonists. Synthesis and Biological Activity of Benzimidazolecarboxylic Acids[1]

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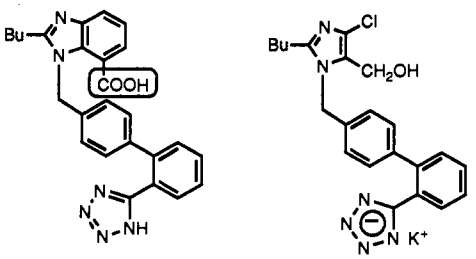
A series of 2-substituted-1-[(biphenyl-4-yl)methyl]-1*H*-benzimidazole-7-carboxylic acids was prepared from the key intermediate 3-amino-2-[[(biphenyl-4-yl)methyl]amino]benzoate (**6a–c**) in order to clarify the structure–activity relationships of various analogues of 2-butyl-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-carboxylic acid (CV-11194), a potent and long acting angiotensin II (AII) receptor antagonist. The AII antagonistic activity of the benzimidazoles was investigated by *in vitro* assays, which included an AII receptor binding assay and AII-induced vasocontraction assay, as well as by *in vivo* assays such as an AII-induced pressor response in rats. Most of the benzimidazoles showed high affinity for the AII receptor (IC_{50} value, 10^{-6}–10^{-7} M) and inhibited the AII-induced pressor response at 1 or 3 mg/kg po, and the effects were more potent than those of CV-11194 and DuP 753. The structure–activity relationship studies on the binding affinity and the inhibition of AII-induced pressor response suggested that straight chains of a certain length (e.g., ethoxy groups, ethyl groups) were the best as substituents at the 2-position and that their steric factors, lipophilicity, and electronic effects affected the potency of the AII antagonistic action. Both a carboxyl group at the 7-position and a tetrazole ring at the 2′-position were particularly important for potent and orally active AII antagonistic activity and a long-acting hypotensive effect. The representative compound, 2-ethoxy-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-carboxylic acid (**26b**, CV-11974), inhibited the specific binding of [^{125}I]AII to bovine adrenal cortical membrane with an IC_{50} value of 1.1×10^{-7} M. The AII-induced contraction of rabbit aortic strips was antagonized by CV-11974 (IC_{50} value, 3.0×10^{-10} M). Oral administration of CV-11974 to conscious normotensive rats at 1 mg/kg resulted in long-lasting inhibition of the AII-induced pressor response. CV-11974 at 0.1–1 mg/kg iv reduced blood pressure dose-dependently in spontaneously hypertensive rats.

Introduction

The renin–angiotensin system (RAS) has been demonstrated to play an important role in the regulation of blood pressure and fluid volume homeostasis.[2] Compounds that interfere with this system can be effective for the treatment of hypertension and congestive heart failure. Angiotensin coverting enzyme inhibitors such as captopril and enalapril work by preventing the production of angiotensin II (AII) from angiotensin I and are the only class currently used clinically. AII is the primary effector hormone in the RAS, and the functions of AII are mediated through specific receptors on cell membranes. Recently attention has been focused on nonpeptide AII receptor antagonists which are expected to provide effective pharmacological action by blocking the RAS at the final step.[3]

In our previous report, we described the discovery of novel nonpeptide AII receptor antagonists 2-butyl-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-carboxylic acid (CV-11194) (Figure 1) and its analogues which are more potent and longer acting orally active AII receptor antagonists than DuP 753.[4] Herein, we report the synthesis, biological evaluation, and structure–activity relationships (SAR) of a series of 1-[(biphenyl-4-yl)methyl]-1*H*-benzimidazole-7-carboxylic acids bearing a variety of substituents at the 2-position of the benzimidazole ring. Although an alkyl side chain is one of the common features of the AII receptor antagonists reported so far, there are only a limited number of reports on the quantitative structure–activity relationships (QSAR) with respect to this side chain.[3a,b]



CV-11194 DuP 753 (losartan)

Figure 1.

Chemistry

The compounds prepared for this study are shown in Table I, and the synthetic methods are outlined in Schemes I–VI.

Convenient starting materials for the synthesis of 2-substituted benzimidazole-7-carboxylic acids were determined to be methyl or ethyl 3-amino-2-[[2′-(substituted)biphenyl-4-yl]methyl]aminobenzoates (**6a–c**), which were prepared from commercially available 3-nitrophthalic acid (1) as shown in Scheme I. Acid-catalyzed esterifi-

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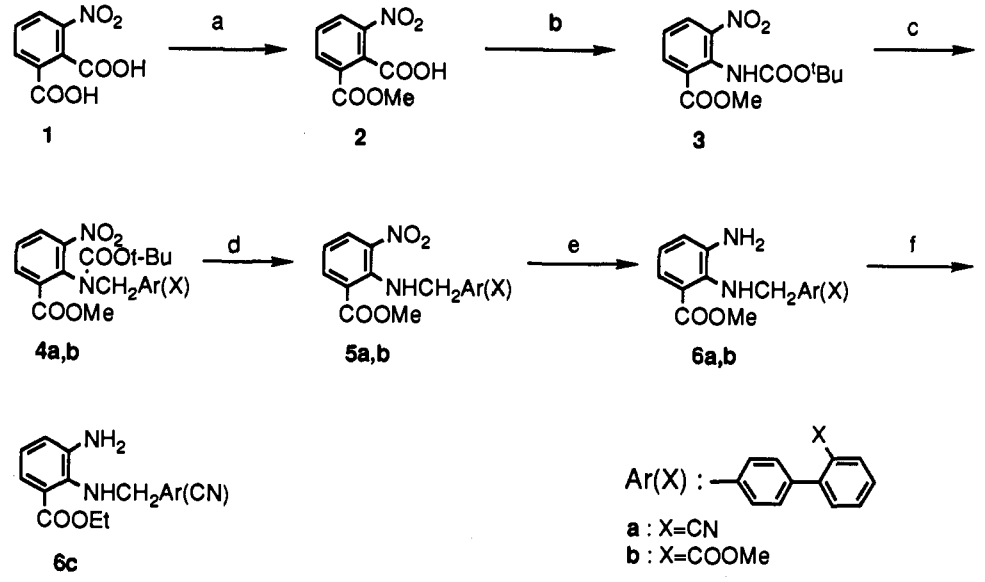
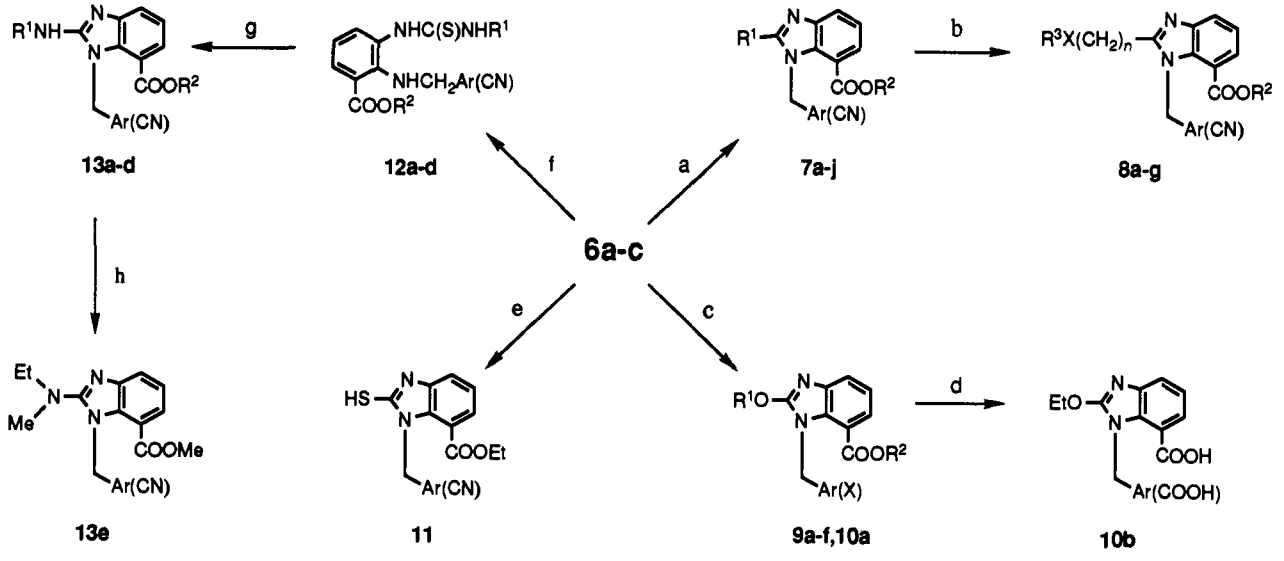
Scheme I[a]



[a] (a) concd H_2SO_4, MeOH, $CH(OMe)_3$; (b) (1) $SOCl_2$, (2) NaN_3, (3) *t*-BuOH; (c) $BrCH_2Ar(X)$, K_2CO_3, CH_3CN; (d) 1 N HCl; (e) $H_2NNH_2 \cdot H_2O$, $FeCl_3$/C, THF–MeOH; (f) EtONa, EtOH.

Scheme II[a]



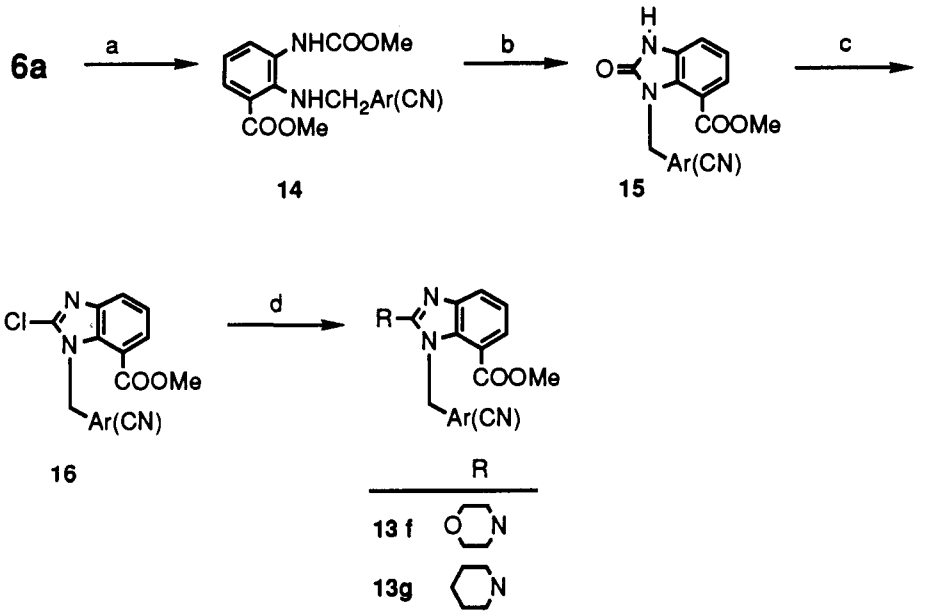
[a] (a) (1) R^1COCl, Et_3N or $(s\text{-BuCO})_2O$, Py, (2) concd HCl, MeOH; (b) (1) R^3XH, base, (2) concd H_2SO_4, MeOH; (c) $(R^1O)_4C$, AcOH; (d) 1 N NaOH; (e) $EtOCS_2K$, EtOH; (f) R^1NCS, EtOH; (g) MeI; (h) NaH, MeI.

cation of 1 in the presence of trimethyl orthoformate was followed by Curtius rearrangement using the standard procedure, and the intermediate isocyanate was coupled to *tert*-butyl alcohol to give the urethane **3**. Alkylation of **3** was accomplished with 4-(bromomethyl)biphenyls[4b] followed by deprotection with 1 N HCl to afford the 3-nitro-2-[[2′-(substituted)biphenyl-4-yl]methyl]aminobenzoates (**5a,b**) in 53–77% yields. Compounds **5a,b** were reduced to **6a** or **6b** with hydrazine hydrate and a catalytic amount of ferric chloride in 64–79% yields.[5] Reduction of **5a,b** over palladium/carbon or Raney nickel catalysts gave poorly reproducible results because of partial debenzylation. Ethyl ester **6c** was prepared by treatment of **6a** with sodium ethoxide.

2-Substituted benzimidazoles **7–11** and **13** were synthesized from **6a–c** as shown in Scheme II. Acylation of **6a** or **6c** with acyl chloride or acyl anhydride in the presence of triethylamine followed by heating with concentrated HCl in MeOH gave 2-alkylbenzimidazoles **7a–h** in good to excellent yields. The reactions with chloroacetyl chloride and 3-chloropropionyl chloride were conducted at room temperature without base to give 2-(chloromethyl)- (**7i**) and 2-(2-chloroethyl)benzimidazole **7i** and **7j**, respectively. Substitution reactions of **7i** or **7j** bearing an ω-chloroalkyl group at the 2-position with several nucleophiles (MeO^-, EtO^-, MeSH, EtSH, and AcO^-) formed 2-(substituted alkyl)benzimidazoles **8a–g** in 52–93% yields. 2-Alkoxybenzimidazoles **9a–f** and **10a** were prepared according to the known method using tetraalkoxymethane[6] and acetic acid in 68–90% yields.[7] The diester compound **10a** was hydrolyzed to the dicarboxylic acid **10b**. The reaction of potassium *O*-ethyldithiocarbonate with **6c** afforded a 2-mercaptobenzimidazole derivative **11**. Addition of **6a** or **6c** to alkyl isothiocyanates followed by S-methylation and cyclization gave 2-(alkylamino)benzimidazoles **13a–d**. Methylation of **13b** with methyl iodide and sodium hydride produced a 2-(*N*-ethyl-*N*-methylamino) analogue **13e**.

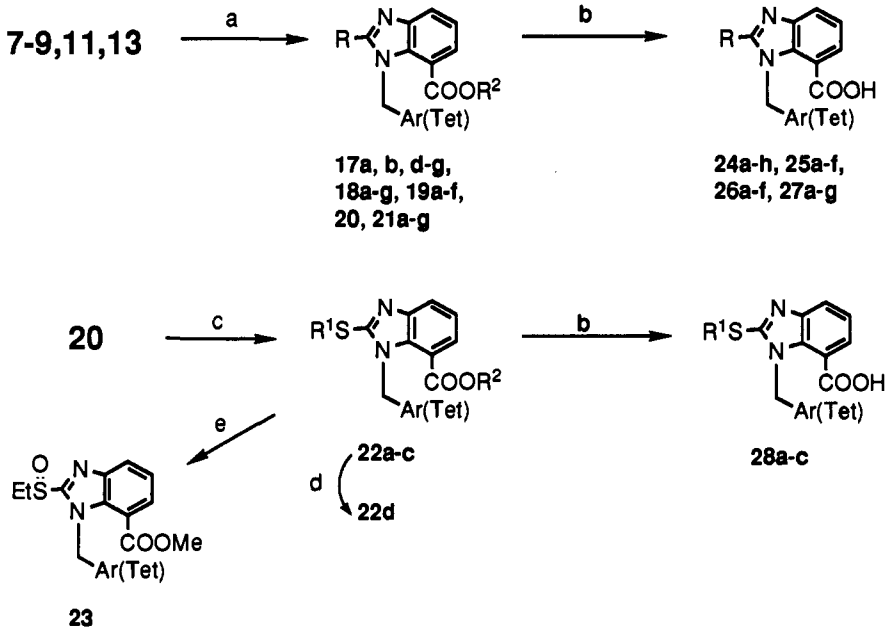
Introduction of cyclic amines at the 2-position was accomplished by the reaction of piperidine or morpholine

Scheme III[a]



[a] (a) ClCOOMe, Py; (b) MeONa, reflux; (c) $POCl_3$, reflux; (d) morpholine or piperidine.

Scheme IV[a]



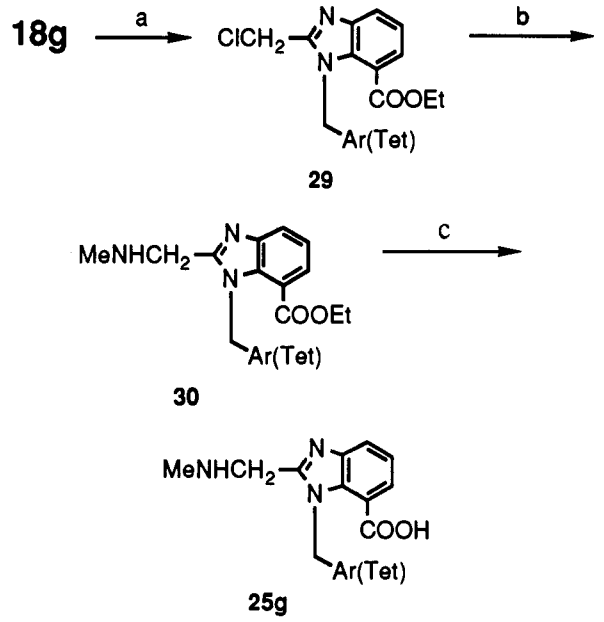
[a] (a) NaN_3, NH_4Cl or (1) Me_3SnN_3, (2) 1 N HCl; (b) 1 N NaOH or $LiOH \cdot H_2O$; (c) R^1I, 1 N NaOH; (d) NaOMe; (e) *m*-CPBA.

with the 2-chlorobenzimidazole derivative **16**, which was prepared from **6a** by methoxycarbonylation, base-catalyzed cyclization, and reaction with phosphorus oxychloride ($POCl_3$) (Scheme III). The cyano group of **7–9, 11,** and **13** was converted to a tetrazole ring (**17–21**) with NaN_3/NH_4Cl or trimethyltin azide (Me_3SnN_3). In the case of methyl 2-alkylbenzimidazole-7-carboxylates **7c,h**, the methyl ester group was hydrolyzed during the reaction with NaN_3/NH_4Cl. S-Alkylation of **20** with alkyl iodides gave 2-(alkylthio)benzimidazoles **22a–c**. The ester **22b** was treated with sodium methoxide followed by oxidation to give sulfoxide **23**. Alkaline hydrolysis of **17–22** gave the desired carboxylic acids **24–28** (Scheme IV).

2-[(Methylamino)methyl]benzimidazole **25g**, which could not be obtained via ethyl 1-[(2′-cyanobiphenyl-4-yl)-methyl]-2-[(methylamino)methyl]-1*H*-benzimidazole-7-carboxylate because of unsuccessful tetrazole ring formation, was synthesized as shown in Scheme V. 2-(Hydroxymethyl)benzimidazole **18g**, bearing a [2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl moiety, was converted to the 2-chloromethyl analogue **29** followed by substitution with methylamine to give the (methylamino)methyl analogue **30**, which was hydrolyzed to afford the carboxylic acid **25g**.

The regioisomers of the carboxylic acid **26b** were prepared as shown in Scheme VI. Cyclization of methyl diaminobenzoate (**31**)[8] with tetraethoxymethane was followed by alkylation to furnish mixtures of regioisomers (**33a**:**33d** = 3:1, **33b**:**33c** = 1:1) which were separated by column chromatography. Each of the esters **33a–c** was detritylated with 1 N HCl, and the structure of each product was assigned by NOE difference spectra. Irradiation of the benzyl protons at δ 5.33 in **34c**, the 6-carboxylate isomer, caused enhancement of the H-7 peak

Scheme V[a]



[a] (a) $SOCl_2$, CH_2Cl_2; (b) $MeNH_2$, CH_3CN, 60 °C; (c) 1 N NaOH, MeOH, reflux.

at δ 7.98 (dd, J = 0.7 and 1.6 Hz), and the NOE also extended to the doublet of H-3 and H-5 in the biphenyl part. By contrast, irradiation of the benzyl protons at δ 5.27 in **34b**, the 5-carboxylate isomer, resulted in enhancement of the H-7 proton which appeared at δ 7.49 (dd, J = 0.7 and 8.4 Hz). This evidence supports our assignment. Compounds **34a–c** were hydrolyzed to give the corresponding carboxylic acids **35a–c**.

Pharmacological Results

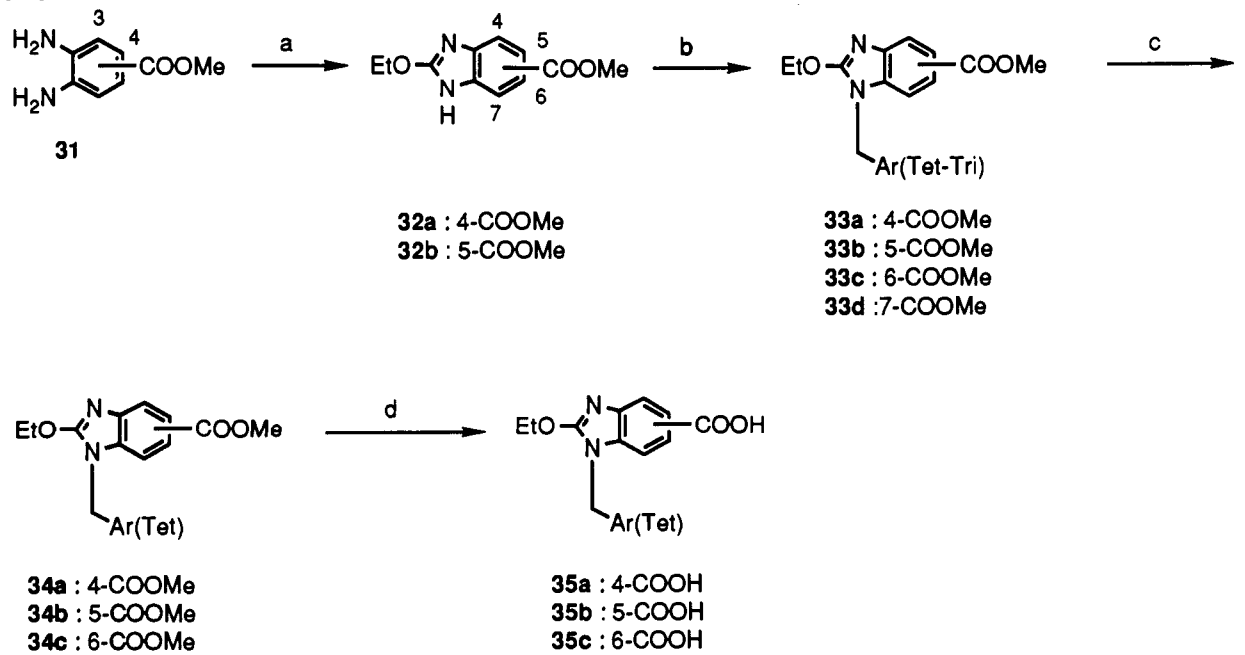
Each compound was evaluated for the binding affinity to the AII receptor with respect to the inhibition of [^{125}I]-AII (0.2 nM) binding to bovine adrenal cortical membranes as described previously.[4] The results were expressed as IC_{50} values (concentration required to inhibit 50% of the binding of [^{125}I]AII).

Many compounds were found to have IC_{50} values in the range of 10^{-6}–10^{-7} M (Table I). The effects of varying the side chain (R) at the 2-position of the benzimidazole ring on binding affinity were examined. We found that the optimal length of R seemed to be two or three atoms (C, N, O, and S) regardless of the nature of R and that straight side chains were generally superior to branched side chains (**24f,g, 27e–g**). The modification of the carboxylic acids to the corresponding esters led to a small decrease in binding affinity (**26a** vs **19a**, **26c** vs **19c**, and **26d** vs **19f**). Replacement of the tetrazole ring with a carboxyl group (**10b**) resulted in slight reduction in binding affinity (Table I).[4] Comparison of binding affinities among the carboxylic acids **26b** and **35a–c** revealed that the position of the carboxyl group was very important, as we pointed out in our previous report[4] (Table II).

The importance of the position of the carboxyl group (**26b, 35a–c**) was also demonstrated in the case of inhibition of AII-induced contraction in rabbit aortic strips. As shown in Figure 2 and Table II, the inhibitory effect of 7-carboxylic acid **26b** was more potent than that of other carboxylic acids (**35a–c**) by 1–3 orders of magnitude.

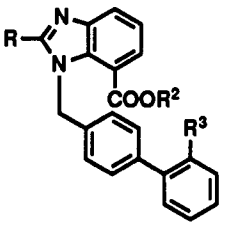
The compounds were further evaluated *in vivo* for inhibition of the pressor response induced by AII (100 ng/kg iv) in conscious rats, and the data are listed in Tables I and II. Varying R was found to cause effects on inhibitory activity similar to those on binding affinity. The optimum activities were found to be associated with a chain length of two or three atoms (C, N, O, and S) regardless of the nature of R. Branching of the alkyl side chain resulted in a decrease in the potency (**24d,f,g**). With regard to the nature of R, substituted alkyl groups seemed to be inferior to other groups. The nature of R also influenced the duration of action. For example, **28a–c** had a shorter duration of action than **24a–c** or **26a–c** at low doses (data not shown). This might be explained by oxidative metabolism to produce less potent alkyl sulfoxide derivatives like **23**. Shorter duration of action was also observed in the case of **25a–c**. In term of inhibitory potency, immediate onset of action, and duration of action, alkoxy

Scheme VI[a]



[a] (a) $(EtO)_4C$, AcOH, 80 °C; (b) (1) NaH, (2) $BrCH_2Ar$(Tet-Tri); (c) 1 N HCl; (d) 1 N NaOH.

Table I. Inhibitory Effects of AII Receptor Antagonists on Specific Binding of [^{125}I]AII and Pressor Response Induced by AII in Rats



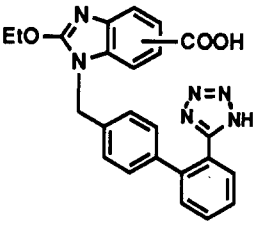
compd	R	R²	R³	IC_{50}[a] (× 10^{-7} M)	% inhibition at 3 h/7 h[b] 1 mg/kg po	3 mg/kg po
10b	EtO	H	CO_2H	1.9	26/44	37/49
19a	MeO	Me	Tet[c]	4.9	94/89	NT
19b	EtO	Me	Tet	0.66	100/90	100/100
19c	PrO	Et	Tet	10	NT	66/93
19d	BuO	Me	Tet	>10	NT	NT
19e	CH_2=$CHCH_2O$	Me	Tet	8.5	14/12	NT
19f	CF_3CH_2O	Me	Tet	>10	36/9	NT
22d	EtS	Me	Tet	4.4	NT	NT
23	EtS(O)	Me	Tet	>10	NT	NT
24a	Me	H	Tet	1.9	NT	50/51
24b	Et	H	Tet	0.46	79/62	96/95
24c	Pr	H	Tet	1.7	83/69	90/91
24d	*i*-Pr	H	Tet	0.82	NT	61/38
24e	c-Pr	H	Tet	0.84	80/88	92/96
24f	*s*-Bu	H	Tet	39	6/0	15/18
24g	*i*-Bu	H	Tet	32	-9/13	29/29
24h	Pen	H	Tet	5.6	NT	32/40
25a	$MeOCH_2$	H	Tet	2.5	47/33	NT
25b	$EtOCH_2$	H	Tet	4.4	63/29	NT
25c	$MeSCH_2$	H	Tet	1.5	85/44	NT
25d	$EtSCH_2$	H	Tet	3.0	68/57	NT
25e	$MeOCH_2CH_2$	H	Tet	5.8	13/3	NT
25f	$MeSCH_2CH_2$	H	Tet	6.2	10/10	NT
25g	$MeNHCH_2$	H	Tet	8.0	42/50	NT
26a	MeO	H	Tet	0.32	97/80	NT
26b (CV-11974)	EtO	H	Tet	1.1	100/92	100/100
26c	PrO	H	Tet	1.9	87/83	100/100
26d	CF_3CH_2O	H	Tet	5.8	28/7	NT
27a	MeNH	H	Tet	1.7	28/49	NT
27b	EtNH	H	Tet	0.62	81/85	100/100
27c	PrNH	H	Tet	0.39	46/66	73/72
27d	BuNH	H	Tet	6.5	38/19	52/61
27e	EtNMe	H	Tet	>10	NT	NT
27f	morpholino	H	Tet	>10	NT	NT
27g	piperidino	H	Tet	>10	NT	NT
28a	MeS	H	Tet	1.2	100/81	100/95
28b	EtS	H	Tet	1.7	87/90	99/97
28c	PrS	H	Tet	1.2	100/100	88/76
CV-11194	Bu	H	Tet	5.5	49/53	80/76
DuP 753				1.5	21/34	62/74

[a] Inhibition of specific binding of [^{125}I]AII (0.2 nM) to bovine adrenal cortex. The IC_{50} value is the concentration of compound which inhibits [^{125}I]AII binding by 50%. Assays were performed in duplicate. Intraassay and interassay IC_{50} values for a given compound may vary less than 3% and less than 10%, respectively. For **26b** (CV-11974) the IC_{50} (×10^{-7} M) ± SEM is 1.1 ± 0.1 (n = 3). [b] Percent inhibition of the AII (0.1 μg/kg iv) induced pressor response at 3 and 7 h after administration of the test compounds in conscious male Sprague-Dawley rats. The inhibition of the pressor response to AII was calculated from duplicate experiments except **26b** (n = 3) and DuP 753 (n = 3). The inhibitory effect (% inhibition) may vary less than 30%. The data in Figure 2 are indicative of the variation measured throughout this study. NT means "not tested". [c] Tet: tetrazol-5-yl.

derivatives **19a,b** and **26a–c** were superior to others (Figure 3 and Table I).

The position of the carboxyl group was found to have a pronounced effect on the inhibitory activity (Table II). Among regioisomers **26b** and **35a–c**, the best result was obtained with 7-carboxylic acid **26b**. Whereas 4- or 5-carboxylic acids **35a,b** had little inhibitory activity at 10 mg/kg po, **26b** at the same dose caused complete inhibition for longer than 7 h.

Table II. Inhibitory Effects of 2-Ethoxybenzimidazoles on Specific Binding of [^{125}I]AII to Bovine Adrenal Cortex, AII-Induced Rabbit Aorta Strips Contraction, and AII-Induced Pressor Responses in Rats



compd	position of COOH	receptor binding IC_{50}[a] (× 10^{-7} M)	aortic contraction IC_{50}[b] (× 10^{-10} M)	% inhibition of pressor response 10 mg/kg po[c] 3 h	7 h
35a	4	450	1310	22	5
35b	5	130	1910	4	4
35c	6	9.3	19	50	34
26b	7	1.1	2.0	100	100

[a] See footnote *a* in Table I. [b] IC_{50} values in rabbit aorta strips (n = 6–8) contracted with AII (1 × 10^{-8} M). Concentration–inhibition curves were linear, where correlation coefficients were 0.94–0.99. [c] See footnote *b* in Table I.

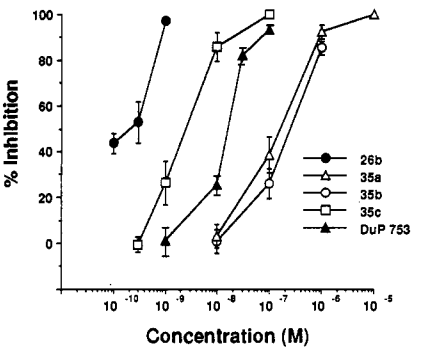


Figure 2. Concentration–inhibition curves of benzimidazole-carboxylic acids and DuP 753 on the AII (10 nM) induced contraction in isolated rabbit aorta (n = 6–8).

Significant improvement in inhibitory activity was realized when a carboxyl group on the biphenyl moiety was replaced with a tetrazole ring (**10b** vs **26b**) (Table I). Similar improvement has been noted with other nonpeptide AII antagonists.[3b]

In consideration of its inhibitory potency, immediate onset of action, and duration of action, 2-ethoxy-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-carboxylic acid (**26b**) was selected for more extensive studies under the code name CV-11974.

Biological Activities of CV-11974

As shown in Figure 4, oral administration of CV-11974 at 1 mg/kg produced almost complete inhibition of the pressor response induced by AII (100 ng/kg iv) in conscious normotensive rats. The inhibitory activity of CV-11974 was more potent and longer acting than that of its prototype, CV-11194, and DuP 753.

In spontaneously hypertensive rats (SHR), CV-11974 at 0.1–1 mg/kg iv significantly decreased blood pressure in a dose-dependent manner and was more potent than EXP 3174, an active metabolite of DuP 753[3a] (Figure 5). A single dose of CV-11974 at 1 mg/kg iv reduced the mean

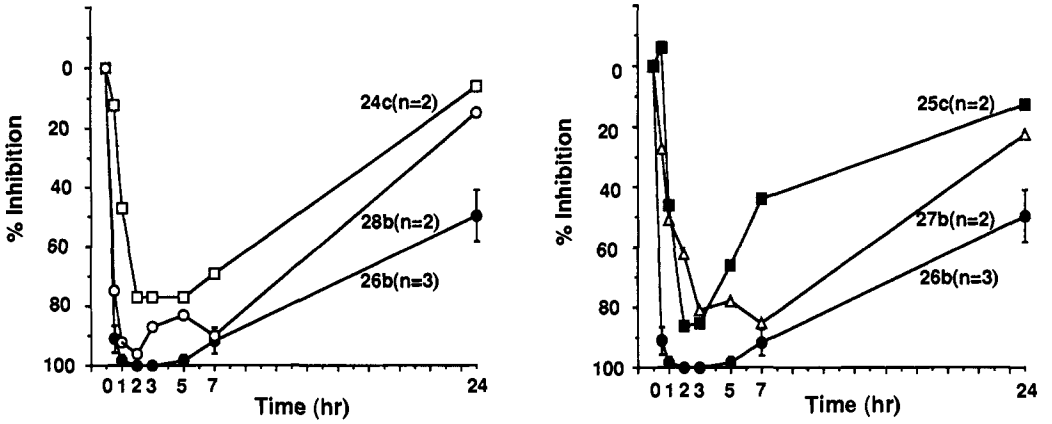


Figure 3. Inhibitory effects of benzimidazoles (1 mg/kg po) on AII (100 ng/kg iv) induced pressor response in conscious normotensive rats. The number of experiments is shown in parentheses.

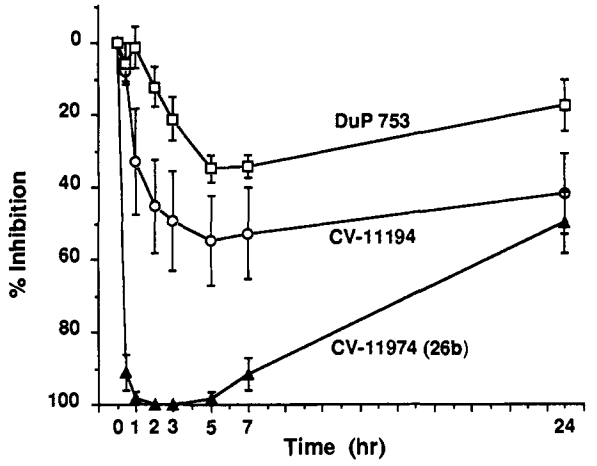


Figure 4. Inhibitory effects of CV-11974 (**26b**), CV-11194, and DuP 753 (1 mg/kg po, n = 4–5) on AII (100 ng/kg iv) induced pressor response in conscious normotensive rats.

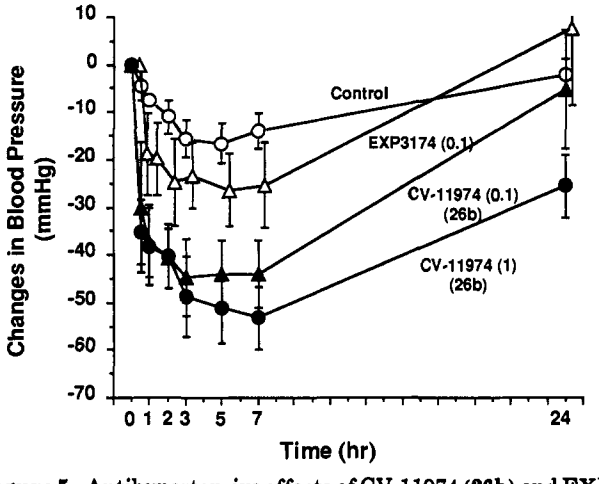


Figure 5. Antihypertensive effects of CV-11974 (**26b**) and EXP 3174 (0.1 or 1 mg/kg iv) in conscious SHR (n = 4–5).

arterial blood pressure by more than 50 mmHg with a duration of action exceeding 24 h. It produced no observable alteration in the basal heart rate at these doses (data not shown).

CV-11974 selectively inhibited the AII-induced contraction of rabbit aortic strips in a noncompetitive manner; it had no effects on the contraction induced by norepinephrine, KCl, serotonin, prostaglandin $F_{2\alpha}$, or endothelin.[9] CV-11974 is also an insurmountable AII antagonist.[10]

Table III. π and ν Values of R and Comparison of log ($1/IC_{50}$) and Calculated Values

compd	R	π^a	ν^b	log ($1/IC_{50}$) exptl	log ($1/IC_{50}$) calcd	Δ log ($1/IC_{50}$)
24a	Me	0.56	0.52	6.71	7.15	−0.44
24b	Et	1.02	0.56	7.34	7.04	0.30
24c	Pr	1.55	0.68	6.77	6.65	0.12
24d	*i*-Pr	1.53	0.76	7.09	6.52	0.57
CV-11194	Bu	2.00[c]	0.68	6.26	6.36	−0.10
24f	*s*-Bu	2.04	1.02	5.41	5.74	−0.33
24g	*i*-Bu	2.03[c]	0.98	5.49	5.82	−0.33
24h	Pen	2.50[c]	0.68	6.25	5.91	0.34
25a	$MeOCH_2$	−0.78	0.63	6.60	6.36	0.24
25b	$EtOCH_2$	−0.28[c]	0.61	6.36	6.74	−0.38
25e	$MeOCH_2CH_2$	−0.28[c]	0.89	6.24	6.26	−0.02
26a	MeO	−0.02	0.36	7.50	7.29	0.21
26b (CV-11974)	EtO	0.38	0.48	6.96	7.19	−0.23
26c	PrO	1.05	0.56	6.72	7.04	−0.32
27a	MeNH	−0.47	0.39	6.77	7.01	−0.24
27b	EtNH	0.08	0.59	7.21	6.93	0.28
27c	PrNH	0.58[c]	0.64	7.41	6.94	0.47
27d	BuNH	1.45	0.70	6.19	6.66	−0.47
28a	MeS	0.61	0.64	6.91	6.94	−0.03
28b	EtS	1.07	0.94	6.77	6.38	0.39
28c	PrS	1.57[c]	1.07	5.92	5.96	−0.04

[a] Hansch's lipophilic parameter of R (Craig, P. N. *J. Med. Chem.* 1974, *14*, 680.). [b] Steric parameter (Charton, M. *Design of Biopharmaceutical Properties through Prodrugs and Analogs*; Roche, E. B., Ed.; Am. Pharm. Ass. Acad. Pharm. Sci.: Washington, 1977, Chapter 9.). [c] Estimated values.

Discussion and Conclusion

The effects of the substituent R at the 2-position of the benzimidazole ring on binding affinity were analyzed quantitatively using the Hansch–Fujita method.[11] Equations were derived for the antagonists with the use of the substituent parameters listed in Table III and multiple regression analysis. The steric parameter, ν, seemed to be the most important single parameter, and analysis gave eq 1. A negative correlation for this term in eq 1 showed

$$\log (1/IC_{50}) = 8.04(\pm 0.71) - 2.09(\pm 0.98)\nu \quad (1)$$

$$n = 21,\ r = 0.71,\ s = 3.29,\ F_{1,19} = 19.5\ (F_{1,19;\alpha=0.005} = 10.1)$$

that the 2-position should be accommodated in a small space. The lipophilic parameter, π, was the next term added, and resulting eq 2 has a better correlation coefficient (r = 0.83) than eq 1 (r = 0.71). The addition of other physicochemical parameters gave no improvement. The optimum value (π_0) for π was calculated to be 0.66, which

$$\log (1/IC_{50}) = 7.92(\pm 0.63) + 0.38(\pm 0.38)\pi - 0.29(\pm 0.21)\pi^2 - 1.73(\pm 0.99)\nu \quad (2)$$

$$n = 21,\ r = 0.83,\ \pi_0 = 0.66,\ s = 2.10,\ F_{3,17} = 12.32\ (F_{3,17;\alpha=0.005} = 6.16)$$

corresponds to values for methyl, ethoxy, propylamino, and methylthio groups. This indicates a need for a substituent that is small as well as lipophilic to a certain degree for optimal binding affinity. This is demonstrated in the data by the stronger affinity of compounds with methoxy, ethoxy, ethylamino, propylamino, or methylthio groups compared with more bulky groups or substituted alkyl groups. Table III lists the experimentally determined affinities, such as log ($1/IC_{50}$), and those calculated using eq 2. In each equation, n, r, s, and F represent the number of the compounds used, correlation coefficient, standard deviation, and value in the F test, respectively. The number in parentheses is the 95% confidence interval.

The electronic effects of the substituent R on binding affinity could not be estimated in the above analysis. This may be due to the great contribution of the steric effect. In order to disregard the steric effect, we selected four compounds (**24c**, **26b**, **27b**, **28b**) with similar π values for molecular orbital calculation using MNDO-PM3. We found a satisfactory negative correlation between IC_{50} values and electron distributions (ed) of the highest occupied molecular orbitals (HOMO) at the 3-position (nitrogen atom: N-3) in the benzimidazole ring (eq 3, Table IV, and Figure 6). The finding that a larger ed causes stronger binding suggests that there is some electronic interaction with the binding site which is not adequately explained by eq 2. The binding site may be located near the lipophilic pocket for substituent R. The nitrogen atom may contribute to the antagonist–receptor complex formation by acting as an electron donor in hydrogen bonding.

$$IC_{50} = 3.83(\pm 0.34) - 15.36(\pm 2.01)\text{ed} \quad (3)$$

$$n = 4,\ r = 0.98,\ s = 0.027$$

In our previous report,[4] we presented the functional assignment of the benzimidazole antagonist structure, where the 2-substituent and the biphenyltetrazole moiety were responsible for binding affinity. This QSAR gave further insight into the nature of the interactions of these parts and the AII receptor. As shown in Figure 7, the interactions may be characterized as a hydrogen-bonding interaction caused by N-3, as an ionic interaction caused by the tetrazole ring, and as a hydrophobic interaction caused by the 2-substituent and the biphenyl moiety.

Little correlation was found in case of the SAR of the substituent on the benzene ring of the benzimidazole moiety.[4] On the contrary, a parallel correlation between binding affinity and inhibition of AII-induced pressor response was found in this study on the 2-substituent. This fact supports a different mode of recognition for the substituent on the benzene ring of the benzimidazole moiety and the 2-substituent by the receptor. 2-Alkylamino derivatives **27a–d** possessed moderate inhibitory activity although they had high binding affinities. This decrease in *in vivo* activity may be due to low solubility, which may result in poor oral absorption.

The importance of the position of the carboxyl group was reconfirmed by comparison of AII antagonistic activity of the carboxylic acids **26b** and **35a–c**, which proved the 7-position to be the best position for this group.

The results obtained here and the continuing research on the structure of the AII receptor should supply information that will enable us to design more potent AII antagonists.

In conclusion, from the QSAR, the ethoxy group was found to be the best substituent at the 2-position, and the 2-ethoxy derivative (**26b**: CV-11974) was selected for further evaluation in several models.[9,12] CV-11974 is an orally active AII antagonist which is more potent and has a longer duration of action than CV-11194 or DuP 753.

Table IV. Electron Distribution (ed) of HOMO at N-3 and AII Receptor Affinity (IC_{50})

compd	R[a]	ed[b]	IC_{50} ($\times 10^{-7}$ M) exptl	IC_{50} ($\times 10^{-7}$ M) calcd	ΔIC_{50}
24c	Pr	0.133	1.7	1.8	−0.1
26b	EtO	0.174	1.1	1.2	−0.1
27b	EtNH	0.209	0.62	0.62	±0.0
28b	EtS	0.147	1.7	1.6	0.1

[a] Substituents at the 2-position. [b] Calculated by MNDO-PM3.

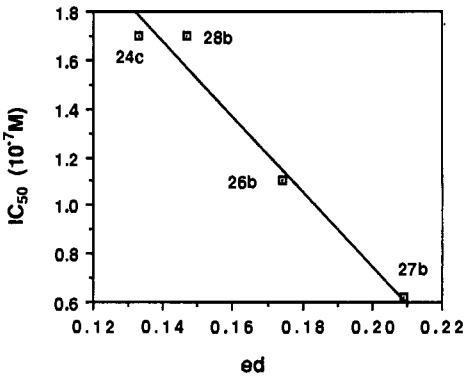


Figure 6. Correlation between electron distribution of HOMO (ed) at N-3 and IC_{50}.

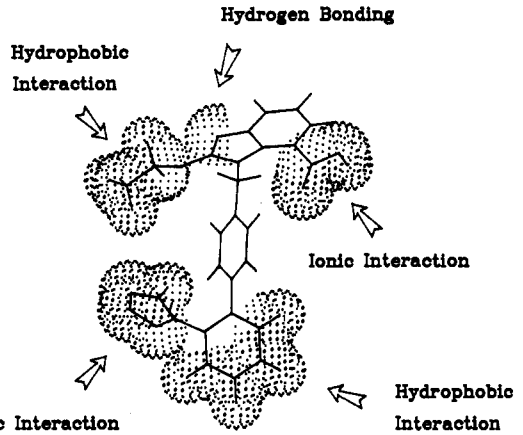


Figure 7. Representation of interactions between the AII antagonists and the AII receptor. The dot clouds indicate the van der Waals surface of each domain.

Experimental Section

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. The infrared (IR) spectra were recorded on a Hitachi 215 grating infrared spectrophotometer. The proton nuclear magnetic resonance (^1H NMR) spectra were recorded on either a Varian Gemini-200 (200 MHz) or an EM-390 (90 MHz) spectrometer. Chemical shifts are given in δ values (ppm) using tetramethylsilane as the internal standard, and coupling constants (J) are given in hertz. Column chromatography was performed using silica gel (Wakogel C-300

or Merck Art 9385). The biological assay was performed as described previously.[4]

The tetraalkoxymethanes were prepared by the method described previously.[6]

Tetraallyloxymethane. The title compound was obtained in 52% yield as a pale yellow oil: bp_{23-24} 120–122 °C; ^1H NMR ($CDCl_3$) δ 4.14 (8 H, dt, J = 5.4 and 1.5), 5.15 (4 H, dq, J = 10.4 and 1.6), 5.30 (4 H, dq, J = 17.2 and 1.8), 5.83–6.02 (4 H, m); IR (neat) 3075, 3020, 2980, 2940, 2880, 1270, 1245, 1110, 1100, 1030, 990 cm^{-1}.

Tetrakis(2,2,2-trifluoroethoxy)methane. The title compound was obtained in 32% yield as a crude product which was used without distillation, because it decomposed during distillation. ^1H NMR ($CDCl_3$) δ 4.14 (q, J = 8.2).

Methyl 2-[(*tert*-Butoxycarbonyl)amino]-3-nitrobenzoate (3). A mixture of **2**[13] (2.3 g, 10 mmol), thionyl chloride (1.8 g, 15 mmol), and DMF (2 drops) in toluene (10 mL) was refluxed for 0.5 h. The solvent was evaporated in vacuo and the residue was dissolved in acetone (10 mL). The solution was added dropwise to an ice-cooled solution of NaN_3 (1.0 g, 15 mmol) in water (10 mL) and stirring was continued for 1 h at the same temperature. The reaction mixture was diluted with water, and the precipitate was collected by filtration and dried. The mixture of the crude azide and *t*-BuOH (10 mL) was gradually warmed and then refluxed for 1.5 h. After evaporation of the solvent in vacuo, the residue was purified by flash column chromatography (EtOAc–hexane = 1:5). The resulting product was recrystallized from MeOH to give **3** (1.7 g, 57%) as pale yellow prisms: mp 95–96 °C; ^1H NMR ($CDCl_3$) δ 1.50 (9 H, s), 3.96 (3 H, s), 7.23 (1 H, t, J = 8.1), 8.10 (1 H, dd, J = 1.7 and 8.1), 8.17 (1 H, dd, J = 1.7 and 8.1); IR (KBr) 3360, 1730, 1705 cm^{-1}. Anal. ($C_{13}H_{16}N_2O_6$) C, H, N.

Methyl 2-[N-(*tert*-Butoxycarbonyl)-N-[(2′-cyanobiphenyl-4-yl)methyl]amino]-3-nitrobenzoate (4a). A mixture of **3** (0.60 g, 2.0 mmol), 4-(bromomethyl)-2′-cyanobiphenyl (0.54 g, 2.0 mmol), and K_2CO_3 powder (0.28 g, 2.0 mmol) in MeCN (10 mL) was refluxed for 4 h. After evaporation of the solvent, the residue was diluted with water and extracted with EtOAc. The extract was washed with water and dried ($MgSO_4$). The solution was concentrated in vacuo and the residue was purified by flash column chromatography (EtOAc–hexane = 1:4 and then 1:2). The resulting product was recrystallized from EtOAc–hexane to give **4a** (0.83 g, 85%) as colorless prisms: mp 153–154 °C; ^1H NMR ($CDCl_3$) δ 1.35 and 1.59 (9 H, 2 s, 7:2), 3.70 and 3.73 (3 H, 2 s, 7:2), 4.63 (1 H, d, J = 14.3), 4.80 (1 H, d, J = 14.3), 7.23–7.29 (3 H, m), 7.39–7.53 (6 H, m), 7.59–7.67 (1 H, m), 7.75 (1 H, dd, J = 1.2 and 7.8), 7.93 and 7.99 (1 H, 2 dd, J = 1.7 and 8.2), 8.05 and 8.11 (1 H, 2 dd, J = 1.7 and 7.9); IR (KBr) 2220, 1700 cm^{-1}. Anal. ($C_{27}H_{25}N_3O_6$) C, H, N.

Methyl 2-[[2′-Cyanobiphenyl-4-yl)methyl]amino]-3-nitrobenzoate (5a). A mixture of **4a** (0.49 g, 1.0 mmol), ca. 30% ethanolic HCl (3 mL), and EtOAc (3 mL) was stirred at room temperature for 1 h. The reaction mixture was concentrated in vacuo and the residue was diluted with MeOH and aqueous $NaHCO_3$. The precipitate was collected by filtration and recrystallized from $CHCl_3$–MeOH to give **5a** (0.30 g, 77%) as yellow needles: mp 140–141 °C; ^1H NMR (DMSO-d_6) δ 3.84 (3 H, s), 4.26 (2 H, m), 6.86 (1 H, t, J = 7.9), 7.46 (2 H, d, J = 8.4), 7.54–7.65 (4 H, m), 7.79 (1 H, dd, J = 1.4 and 7.7), 7.95 (1 H, dd, J = 1.4 and 7.7), 8.05–8.11 (2 H, m), 8.67 (1 H, t, J = 5.5); IR (KBr) 3300, 2210, 1695 cm^{-1}. Anal. ($C_{22}H_{17}N_3O_4$) C, H, N.

Methyl 2-[[[2′-(Methoxycarbonyl)biphenyl-4-yl]methyl]amino]-3-nitrobenzoate (5b). Compound **5b** was prepared from **3** and methyl 4′-(bromomethyl)biphenyl-2-carboxylate via **4b** by the similar procedures for the preparation of **5a**, in overall 53% yield as a yellow syrup: ^1H NMR ($CDCl_3$) δ 3.61 (3 H, s), 3.89 (3 H, s), 4.21 (2 H, d, J = 4.8), 6.72 (1 H, d, J = 8.0), 7.30 (4 H, m), 7.36 (1 H, dd, J = 1.1 and 7.3), 7.42 (1 H, dd, J = 1.6 and 7.4), 7.53 (1 H, dd, J = 1.6 and 7.5), 7.82 (1 H, dd, J = 1.4 and 7.6), 8.00 (1 H, dd, J = 1.7 and 8.3), 8.10 (1 H, dd, J = 1.8 and 7.8); IR (neat) 3310, 1730, 1690 cm^{-1}.

Methyl 3-Amino-2-[[(2′-cyanobiphenyl-4-yl)methyl]amino]benzoate (6a). A mixture of **5a** (100 g, 0.26 mol), $FeCl_3$·$6H_2O$ (1.0 g, 3.7 mmol), and activated carbon (10 g) in a mixture of MeOH (1 L) and THF (500 mL) was refluxed for 30 min, and then hydrazine monohydrate (72 mL, 1.6 mol) was added dropwise slowly to the reaction mixture. The resulting mixture was refluxed for 14 h further and the insoluble material was removed by filtration. The filtrate was concentrated in vacuo, and the residue was diluted with aqueous $NaHCO_3$ and extracted with EtOAc. The extract was washed with brine and dried ($MgSO_4$). The solvent was evaporated in vacuo and the residue was purified by flash column chromatography ($CHCl_3$). The product was recrystallized from IPE to give **6a** (60 g, 64%) as pale yellow needles: mp 110–111 °C; ^1H NMR ($CDCl_3$) δ 3.81 (3 H, s), 3.97 (2 H, brs), 4.23 (2 H, d, J = 6.6), 6.39 (1 H, t, J = 6.6), 6.84–6.93 (2 H, m), 7.26–7.55 (8 H, m), 7.64 (1 H, dt, J = 1.4 and 8.0), 7.77 (1 H, dd, J = 1.4 and 7.8); IR (KBr) 3410, 3350, 2225, 1695 cm^{-1}. Anal. ($C_{22}H_{18}N_3O_2$·$0.1H_2O$) C, H, N.

Methyl 3-Amino-2-[[[2′-(methoxycarbonyl)biphenyl-4-yl]methyl]amino]benzoate (6b). Compound **6b** was prepared from **5b** by the similar procedure for the preparation of **6a** in 79% yield as a pale yellow syrup: ^1H NMR ($CDCl_3$) δ 3.63 (3 H, s), 3.80 (3 H, s), 3.97 (2 H, brs), 4.22 (2 H, d, J = 4.8), 6.40 (1 H, brs), 6.82–6.92 (2 H, m), 7.23–7.44 (7 H, m), 7.53 (1 H, dt, J = 1.5 and 7.5), 7.79–7.83 (1 H, m); IR (neat) 3450, 3360, 1730, 1700 cm^{-1}.

Ethyl 3-Amino-2-[[(2′-cyanobiphenyl-4-yl)methyl]amino]benzoate (6c). Sodium hydride (60% in oil; 0.44 g, 11 mmol) was added portionwise to ice-cooled EtOH (50 mL) and the solution was stirred at the same temperature for 30 min. The methyl ester (**6a**) (4.0 g, 11 mmol) was dissolved in the solution and the resulting mixture was refluxed for 1.5 h. The solvent was evaporated in vacuo, and the residue was diluted with water and extracted with EtOAc. The extract was washed with water and dried ($MgSO_4$). After evaporation of the solvent, the residue was purified by column chromatography ($CHCl_3$). The product was recrystallized from EtOAc–hexane to give **6c** (3.2 g, 78%) as colorless needles: mp 103.5–104.5 °C; ^1H NMR ($CDCl_3$) δ 1.32 (3 H, t, J = 7.2), 4.23 (2 H, s), 4.26 (2 H, q, J = 7.2), 6.90 (2 H, m), 7.35–7.55 (7 H, m), 7.64 (1 H, dt, J = 1.4 and 8.0), 7.76 (1 H, dd, J = 1.4 and 7.6); IR (KBr) 3445, 3350, 2220, 1680 cm^{-1}. Anal. ($C_{23}H_{21}N_3O_2$) C, H, N.

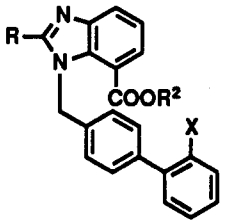
Ethyl 1-[(2′-Cyanobiphenyl-4-yl)methyl]-2-methyl-1*H*-benzimidazole-7-carboxylate (7a). To an ice-cooled solution of **6c** (0.37 g, 1.0 mmol) and triethylamine (0.11 g, 1.1 mmol) in CH_2Cl_2 (5 mL) was added dropwise acetyl chloride (86 mg, 1.1 mmol), and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was washed with aqueous $NaHCO_3$ and dried ($MgSO_4$). The solvent was evaporated in vacuo, and the residue was dissolved in EtOH (3 mL) containing concentrated HCl (0.3 mL). The solution was refluxed for 2.5 h, and the reaction mixture was basified with 2 N NaOH and extracted with EtOAc. The extract was washed with aqueous $NaHCO_3$ and dried ($MgSO_4$). The solvent was evaporated in vacuo and the residue was purified by flash column chromatography ($CHCl_3$–EtOAc = 1:1). The product was recrystallized from EtOAc to give **7a** (0.29 g, 73%) as colorless needles: mp 170–171 °C; ^1H NMR ($CDCl_3$) δ 1.21 (3 H, t, J = 7.1), 2.65 (3 H, s), 4.22 (2 H, q, J = 7.1), 5.85 (2 H, s), 6.99 (2 H, d, J = 8.4), 7.27 (1 H, t, J = 7.8), 7.38–7.47 (4 H, m), 7.57–7.77 (3 H, m), 7.92 (1 H, dd, J = 1.1 and 7.9); IR (KBr) 2210, 1700 cm^{-1}.

7b–e,g–j were prepared by a procedure similar to that described above, and the results are shown in Table V. In the cases of **7i,j**, the acylations of **6a** or **6b** were performed without base.

Ethyl 1-[(2′-Cyanobiphenyl-4-yl)methyl]-2-(2-methylpropyl)-1*H*-benzimidazole-7-carboxylate (7f). A mixture of **6c** (1.1 g, 3.0 mmol) and 2-methylbutyric anhydride (0.56 g, 3.0 mmol) in pyridine (2 mL) was stirred at 115 °C for 15 h. The reaction mixture was diluted with EtOAc and washed successively with dilute HCl and aqueous $NaHCO_3$. After the solvent was evaporated in vacuo, the residue was dissolved in EtOH (15 mL) containing concentrated HCl (0.5 mL), and the solution was refluxed for 3 h. The reaction mixture was concentrated in vacuo, basified with aqueous $NaHCO_3$, and extracted with EtOAc. The extract was washed with water and dried ($MgSO_4$). The solvent was evaporated in vacuo to give **7f** (1.2 g, 92%) as a yellow syrup: ^1H NMR ($CDCl_3$) δ 0.90 (3 H, t), 1.20 (3 H, t), 1.40 (3 H, d), 1.50–2.10 (1 H, m), 4.17 (2 H, q), 5.87 (2 H, s), 6.97 (2 H, d), 7.17–8.03 (9 H, m); IR (neat) 2220, 1710 cm^{-1}.

Methyl 1-[(2′-Cyanobiphenyl-4-yl)methyl]-2-(methoxymethyl)-1*H*-benzimidazole-7-carboxylate (8a). A solution of

Table V. Physicochemical Data of 1-[[2′-Cyano- or 1-[(2′-(Ethoxycarbonyl)biphenyl-4-yl]methyl]-1*H*-benzimidazoles



compd	R	R²	X	synthetic method[a]	% yield	recryst solvent[b]	mp °C	formula[c]
7a	Me	Et	CN	A	73	A	170–171	$C_{25}H_{21}N_3O_2$
7b	Et	Et	CN	A	71	A	164–165	$C_{26}H_{25}N_3O_2$
7c	Pr	Me	CN	A	73	B	134–135	$C_{26}H_{25}N_3O_2$
7d	*i*-Pr	Et	CN	A	62	B	114–115	$C_{27}H_{25}N_3O_2$
7e	c-Pr	Me	CN	A	77	B	154–155	$C_{26}H_{21}N_3O_2$
7f	*s*-Bu	Et	CN	B	92		syrup[d]	
7g	*i*-Bu	Et	CN	A	95		syrup[d]	
7h	Pen	Me	CN	A	55	B	100–101	$C_{28}H_{27}N_3O_2$
7i	$ClCH_2$	Et	CN	C	76	B	180–181	$C_{25}H_{20}ClN_3O_2$
7j	$ClCH_2CH_2$	Me	CN	C	quant.		syrup[d]	
9a	MeO	Me	CN	D	70	D	149–150	$C_{24}H_{19}N_3O_3$
9b	EtO	Me	CN	D	86	A	169–170	$C_{25}H_{21}N_3O_3$
9c	PrO	Et	CN	D	68	B	91–92	$C_{27}H_{25}N_3O_3$
9d	BuO	Me	CN	D	75	D	74–75	$C_{27}H_{25}N_3O_3$
9e	allyl-O	Me	CN	D	73	B	118–119	$C_{26}H_{21}N_3O_3$
9f	CF_3CH_2O	Me	CN	D	20	B	143–145	$C_{25}H_{18}F_3N_3O_3$
10a	EtO	Me	COOMe	D	72	B	112–113	$C_{26}H_{24}N_2O_5$
13a	MeNH	Me	CN	E	42		syrup[d]	
13b	EtNH	Me	CN	E	32	B	135–136	$C_{25}H_{22}N_4O_2$
13c	PrNH	Et	CN	E	65		syrup[d]	
13d	BuNH	Me	CN	E	36		syrup[d]	

[a] Method A: (1) *6*, R^1COCl, Et_3N, CH_2Cl_2, (2) concentrated HCl, MeOH, reflux. Method B: (1) $(Et(Me)CHCO)_2O$, pyridine, CH_2Cl_2, (2) concentrated HCl, MeOH, reflux. Method C: $ClCH_2COCl$ or $ClCH_2CH_2COCl$, room temperature, CH_2Cl_2. Method D: tetraalkoxymethane, AcOH. Method E: (1) *12*, MeI, EtOH, (2) K_2CO_3. [b] A = EtOAc; B = EtOAc–hexane; C = *i*-Pr_2O–EtOAc; D = MeOH. [c] In DMSO-d_6. [c] All compounds gave satisfactory analyses (C, H, N). [d] The products were used without further purification.

7i (0.80 g, 1.9 mmol) and NaOMe (28% MeOH solution; 1.08 g, 5.6 mmol) in MeOH (15 mL) was refluxed for 2 h. The reaction mixture was concentrated in vacuo to dryness and the residue was partitioned between CH_2Cl_2 and water. The organic layer was separated, washed with water, and dried ($MgSO_4$). After evaporation of the solvent, the residue was purified by column chromatography to give **8a** (0.40 g, 52%) as a yellow syrup: ^1H NMR ($CDCl_3$) δ 3.43 (3 H, s), 3.72 (3 H, s), 4.78 (2 H, s), 5.97 (2 H, s), 6.99 (2 H, d), 7.25–7.49 (5 H, m), 7.55–7.77 (3 H, m), 7.99 (1 H, dd).

Methyl 1-[(2′-Cyanobiphenyl-4-yl)methyl]-2-(ethoxymethyl)-1*H*-benzimidazole-7-carboxylate (8b). Sodium metal (0.11 g) was dissolved in EtOH (15 mL), and then **7i** (1.0 g, 2.3 mmol) was added. After the resulting solution was heated at 80 °C for 3 h, 1 N NaOH (2.5 mL) was added to the reaction mixture, and refluxing was continued for 3 h. The reaction mixture was concentrated in vacuo to dryness and the residue was dissolved in water. The aqueous solution was acidified with concentrated HCl, and the precipitate was collected by filtration and dried to give 1-[(2′-cyanobiphenyl-4-yl)methyl]-2-(ethoxymethyl)-1*H*-benzimidazole-7-carboxylic acid (0.95 g, 99%) as a brown powder: ^1H NMR (DMSO-d_6) δ 1.01 (3 H, t), 3.50 (2 H, q), 4.79 (2 H, s), 5.99 (2 H, s), 7.00 (2 H, d), 7.32 (1 H, t), 7.45–7.58 (4 H, m), 7.67–7.78 (2 H, m), 7.88–7.96 (2 H, m).

A solution of the carboxylic acid (0.95 g, 2.3 mmol) and concentrated sulfuric acid (0.15 mL) in MeOH (12 mL) was refluxed for 23 h. The reaction mixture was concentrated in vacuo to dryness and the residue was partitioned between CH_2Cl_2 and water. The organic layer was washed with water and dried ($MgSO_4$). After the solvent was evaporated in vacuo, the residue was purified by column chromatography to give **8b** (0.90 g, 92%) as a pale brown syrup: ^1H NMR ($CDCl_3$) δ 1.16 (3 H, t), 3.59 (2 H, q), 3.72 (3 H, s), 4.82 (2 H, s), 5.99 (2 H, q), 6.99 (2 H, d), 7.24–7.45 (5 H, m), 7.55–7.75 (3 H, m), 7.98 (1 H, dd).

Methyl 1-[(2′-Cyanobiphenyl-4-yl)methyl]-2-[(methylthio)methyl]-1*H*-benzimidazole-7-carboxylate (8c). A mixture of **7i** (1.0 g, 2.3 mmol) and a 15% aqueous solution of sodium methanethiolate (2.2 g, 4.7 mmol) in acetonitrile (20 mL) was stirred at 80 °C for 41 h. The reaction mixture was concentrated in vacuo to dryness. The residue and 1 N NaOH (2.5 mL) were dissolved in EtOH (15 mL), and the solution was refluxed for 3 h. The reaction mixture was concentrated in vacuo to dryness and the residue was dissolved in water. The aqueous solution was acidified with concentrated HCl, and the precipitate was collected by filtration and dried to give 1-[(2′-cyanobiphenyl-4-yl)methyl]-2-[(methylthio)methyl]-1*H*-benzimidazole-7-carboxylic acid (0.99 g, quant.) as pale brown powder: ^1H NMR (DMSO-d_6) δ 2.11 (3 H, s), 4.06 (2 H, s), 5.98 (2 H, s), 6.98 (2 H, d), 7.49 (2 H, d), 7.28 (1 H, t), 7.46–7.80 (4 H, m), 7.87–7.95 (2 H, m).

The carboxylic acid (0.99 g) was esterified by a procedure similar to that described above to give **8c** (0.72 g, 72%) as a yellow syrup: ^1H NMR ($CDCl_3$) δ 2.18 (3 H, s), 3.73 (3 H, s), 3.93 (2 H, s), 5.97 (2 H, s), 7.01 (2 H, d), 7.25–7.33 (1 H, m), 7.39–7.49 (4 H, m), 7.58–7.78 (3 H, m), 7.96 (1 H, dd).

Ethyl 1-[(2′-Cyanobiphenyl-4-yl)methyl]-2-[(ethylthio)methyl]-1*H*-benzimidazole-7-carboxylate (8d). A mixture of **7i** (0.70 g, 1.6 mmol), ethanethiol (0.15 mL, 2 mmol), and potassium carbonate (0.27 g, 2 mmol) in acetonitrile (10 mL) was stirred at room temperature for 1 h and then at 80 °C for another 2 h. The insoluble material was removed by filtration and the filtrate was concentrated in vacuo to dryness. The residue was purified by flash column chromatography to give **8d** (0.65 g, 88%) as an orange syrup: ^1H NMR ($CDCl_3$) δ 1.20 (3 H, t), 1.27 (3 H, t), 2.62 (2 H, q), 3.96 (2 H, s), 4.20 (2 H, q), 6.00 (2 H, s), 7.01 (2 H, d), 7.29 (1 H, t), 7.38–7.49 (4 H, m), 7.57–7.78 (3 H, m), 7.96 (1 H, dd).

Methyl 1-[(2′-Cyanobiphenyl-4-yl)methyl]-2-(methoxyethyl)-1*H*-benzimidazole-7-carboxylate (8e). A mixture of **7j** (1.0 g, 2.3 mmol) and potassium carbonate (0.25 g, 1.8 mmol) in MeOH (30 mL) was refluxed for 2 h and then stirred at room temperature for another 5 h. The solvent was evaporated in vacuo and the residue was dissolved in CH_2Cl_2. The insoluble material was removed by filtration and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography to give **8e** (0.45 g, 59%) as a pale yellow syrup: ^1H NMR ($CDCl_3$) δ 3.19 (2 H, t), 3.34 (3 H, s), 3.72 (3 H, s), 3.92

(2 H, t), 5.88 (2 H, s), 7.00 (2 H, d), 7.26 (1 H, t), 7.40–7.48 (4 H, m), 7.56–7.76 (3 H, m), 7.95 (1 H, dd).

Methyl 1-[(2'-Cyanobiphenyl-4-yl)methyl]-2-[(methylthio)ethyl]-1*H*-benzimidazole-7-carboxylate (8f). A mixture of **7j** (1.1 g, 2.6 mmol) and a 15% aqueous solution of sodium methylthiolate (1.9 g, 4.1 mmol) in acetonitrile (20 mL) was stirred at 60 °C for 2 h. The reaction mixture was concentrated in vacuo and partitioned between water and CH_2Cl_2. The organic layer was separated, washed with water, and concentrated in vacuo to dryness. The residue was purified by flash column chromatography to give **8f** (1.1 g, 93%) as colorless powder: ^{1}H NMR ($CDCl_3$) δ 2.14 (3 H, s), 3.02–3.11 (2 H, m), 3.16–3.25 (2 H, m), 3.74 (3 H, s), 5.86 (2 H, s), 7.00 (2 H, d), 7.28 (1 H, t), 7.39–7.49 (4 H, m), 7.58–7.78 (3 H, m), 7.97 (1 H, dd).

Ethyl 2-(Acetoxymethyl)-1-[(2'-cyanobiphenyl-4-yl)methyl]-1*H*-benzimidazole-7-carboxylate (8g). A mixture of **7j** (2.7 g, 6.3 mmol) and sodium acetate (0.58 g, 7.0 mmol) in DMF (25 mL) was stirred at room temperature for 24 h. The solvent was evaporated in vacuo to dryness and the residue was purified by flash column chromatography to give **8g** (2.9 g, 99%) as a yellow syrup: ^{1}H NMR ($CDCl_3$) δ 1.20 (3 H, t), 1.94 (3 H, s), 4.21 (2 H, q), 5.43 (2 H, s), 6.98 (2 H, d), 7.33 (1 H, t), 7.39–7.48 (4 H, m), 7.57–7.79 (3 H, m), 8.02 (1 H, dd).

Methyl 1-[(2'-Cyanobiphenyl-4-yl)methyl]-2-ethoxy-1*H*-benzimidazole-7-carboxylate (9b). A mixture of **6a** (50 g, 0.14 mol), tetraethoxymethane (45 mL, 0.215 mol), and acetic acid (8.0 mL, 0.14 mol) was stirred at 80–90 °C for 40 min. The reaction mixture was diluted with MeOH (200 mL), and 6 N NaOH (23.5 mL) and H_2O (500 mL) were added. The precipitate was collected by filtration and recrystallized from EtOAc–$CHCl_3$ to give **9b** (53 g, 91%) as colorless prisms: mp 169–170 °C; ^{1}H NMR ($CDCl_3$) δ 1.42 (3 H, t, J = 7.1), 3.71 (3 H, s), 4.63 (2 H, q, J = 7.1), 5.59 (2 H, s), 7.09 (2 H, d, J = 8.4), 7.20 (1 H, t, J = 7.9), 7.45–7.59 (5 H, m), 7.69–7.80 (2 H, m), 7.92 (1 H, dd, J = 1.4 and 7.8). IR (KBr) 2225, 1725, 1040 cm^{-1}.

Compounds **9a,c–f** and **10a** were prepared by a procedure similar to that described above, and the results are shown in Table V.

Ethyl 1-[(2'-Cyanobiphenyl-4-yl)methyl]-2-mercapto-1*H*-benzimidazole-7-carboxylate (11). A solution of **6c** (5.6 g, 15 mmol) and potassium *O*-ethyldithiocarbonate (7.3 g, 45 mmol) in EtOH (50 mL) was refluxed for 8 h. After evaporation of the solvent, the residue was diluted with water and adjusted to pH 3–4 with concentrated HCl. The precipitate was collected by filtration and the product was recrystallized from EtOH to give **11** (5.1 g, 82%) as yellow platelets: mp 225–227 °C; ^{1}H NMR (DMSO-d_6) δ 1.08 (3 H, t, J = 7.1), 4.12 (2 H, q, J = 7.1), 5.90 (2 H, brs), 7.08 (2 H, d, J = 8.2), 7.27 (1 H, t, J = 7.7), 7.38–7.59 (6 H, m), 7.76 (1 H, dt, J = 1.6 and 7.6), 7.92 (1 H, dd, J = 1.6 and 7.6); IR (KBr) 2210, 1720 cm^{-1}. Anal. ($C_{24}H_{19}N_3O_2S$) C, H, N.

Methyl 3-[3-Butyl(thioureido)]-2-[[(2'-cyanobiphenyl-4-yl)methyl]amino]benzoate (12d). A mixture of **6a** (2.5 g, 7.0 mmol) and butyl isothiocyanate (1.2 mL, 10 mmol) in EtOH (15 mL) was stirred at 50 °C for 17 h. The reaction mixture was diluted with water and extracted with EtOAc. The extract was washed with water and dried (Na_2SO_4). After evaporation of the solvent, the residue was purified by flash column chromatography (EtOAc–hexane = 1:3 and then 1:2) to give **12d** (3.3 g, quant.) as a pale yellow syrup: ^{1}H NMR ($CDCl_3$) δ 0.89 (3 H, t, J = 7.2), 1.21–1.39 (2 H, m), 1.45–1.60 (2 H, m), 3.50–3.65 (2 H, brs), 3.92 (3 H, s), 4.56 (2 H, d, J = 5.0), 6.08 (1 H, t, J = 5.0), 6.78 (1 H, t, J = 7.8), 7.21–7.30 (1 H, m), 7.39–7.54 (6 H, m), 7.64 (1 H, dt, J = 1.5 and 7.6), 7.75 (1 H, dd, J = 1.6 and 8.0), 7.98 (1 H, dd, J = 1.6 and 8.0), 8.26 (1 H, brs); IR (neat) 2210, 1690 cm^{-1}.

Compounds **12a–c** were prepared by a procedure similar to that described above. Compound **12a** was used without purification.

Methyl 2-[[(2'-Cyanobiphenyl-4-yl)methyl]amino]-3-[3-ethyl(thioureido)]benzoate (12b). The title compound was obtained in 96% yield as a pale yellow syrup: ^{1}H NMR ($CDCl_3$) δ 1.15 (3 H, t, J = 7.2), 3.60 (2 H, brs), 3.92 (3 H, s), 4.56 (2 H, d, J = 6.4), 6.06 (1 H, t, J = 5.0), 6.79 (1 H, t, J = 7.8), 7.23–7.27 (1 H, m), 7.39–7.54 (6 H, m), 7.60–7.68 (1 H, m), 7.73–7.77 (1 H, m), 7.98 (1 H, dd, J = 1.7 and 7.9), 8.27 (1 H, brs); IR (neat) 2225, 1735, 1690 cm^{-1}.

Ethyl 2-[[(2'-Cyanobiphenyl-4-yl)methyl]amino]-3-[3-propyl(thioureido)]benzoate (12c). The title compound was obtained in 98% yield as a pale yellow syrup: ^{1}H NMR ($CDCl_3$) δ 0.88 (3 H, t, J = 7.4), 1.40 (3 H, t, J = 7.1), 1.40–1.67 (2 H, m), 3.42–3.68 (2 H, brs), 4.37 (2 H, q, J = 7.1), 4.56 (2 H, d, J = 6.4), 6.13 (1 H, t, J = 5.1), 6.78 (1 H, t, J = 7.9), 7.21–7.25 (1 H, m), 7.36–7.53 (6 H, m), 7.64 (1 H, dt, J = 1.4 and 7.7), 7.73–7.77 (1 H, m), 7.99 (1 H, dd, J = 1.6 and 8.0), 8.20–8.40 (1 H, brs); IR (neat) 2220, 1710, 1690 cm^{-1}.

Methyl 2-(Butylamino)-1-[(2'-cyanobiphenyl-4-yl)methyl]-1*H*-benzimidazole-7-carboxylate (13d). A solution of **12d** (3.3 g, 7.1 mmol) and iodomethane (3.5 mL, 56 mmol) in EtOH (30 mL) was refluxed for 24 h. After addition of 1 N HCl (60 mL), the reaction mixture was concentrated in vacuo and extracted with EtOAc. The extract was washed successively with diluted NH_4OH, aqueous NaCl, and dried (Na_2SO_4). The solvent was evaporated in vacuo and the residue was purified by column chromatography (EtOAc–hexane = 1:2 and then 2:1) to give **13d** (1.1 g, 36%) as a pale orange syrup: ^{1}H NMR ($CDCl_3$) δ 0.88 (3 H, t, J = 7.2), 1.20–1.35 (2 H, m), 1.51–1.66 (2 H, m), 3.46–3.56 (2 H, m), 3.74 (3 H, s), 4.22 (1 H, t, J = 5.4), 5.55 (2 H, s), 7.15 (1 H, t, J = 7.8), 7.27 (2 H, d, J = 8.2), 7.40–7.78 (8 H, m); IR (neat) 3400, 3225, 2210, 1710 cm^{-1}.

Compounds **13a–c** were prepared by a procedure similar to that described above, and the results are shown in Table V.

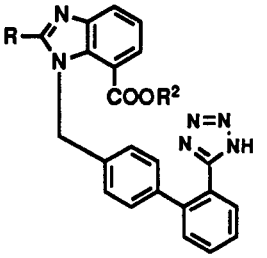
Methyl 1-[(2'-Cyanobiphenyl-4-yl)methyl]-2-(N-ethyl-N-methylamino)-1*H*-benzimidazole-7-carboxylate (13e). To an ice-cooled solution of **13b** (0.95 g, 2.3 mmol) in DMF (5 mL) was added NaH (60% in oil; 0.13 g, 3.25 mmol). The mixture was stirred for 10 min, and then iodomethane (0.2 mL, 3.2 mmol) was added. After the reaction mixture was stirred at the same temperature for 20 min, it was diluted with water and extracted with EtOAc. The extract was washed with water and dried ($MgSO_4$). The solvent was evaporated in vacuo and the residue was purified by flash column chromatography (EtOAc–hexane = 1:2 and then 1:1). The product was recrystallized from EtOAc–hexane to give **13e** (0.80 g, 82%) as colorless needles: mp 66–69 °C; ^{1}H NMR ($CDCl_3$) δ 1.25 (3 H, t, J = 7.1), 3.03 (3 H, s), 3.36 (2 H, q, J = 7.2), 3.73 (3 H, s), 5.60 (2 H, s), 6.88 (2 H, d, J = 8.4), 7.16 (1 H, t, J = 7.8), 7.34–7.49 (5 H, m), 7.59 (1 H, dt, J = 1.6 and 7.7), 7.73 (1 H, dd, J = 1.1 and 7.7), 7.78 (1 H, dt, J = 1.1 and 7.9); IR (KBr) 2210, 1710 cm^{-1}. Anal. ($C_{26}H_{24}N_4O_2 \cdot 0.5H_2O$) C, H, N.

Methyl 2-[[(2'-Cyanobiphenyl-4-yl)methyl]amino]-3-[(methoxycarbonyl)amino]benzoate (14). To an ice-cooled solution of **6a** (10 g, 28.0 mmol) in pyridine (50 mL) was added dropwise methyl chloroformate (9.0 mL, 116 mmol) and the resulting mixture was stirred at room temperature for 3 h. After evaporation of the solvent in vacuo, the residue was diluted with water and extracted with EtOAc. The extract was washed with water and dried (Na_2SO_4). The solvent was evaporated in vacuo and the residue was recrystallized from EtOAc–hexane to give **14** (10.5 g, 90%) as pale yellow needles: mp 113.5–114.5 °C; ^{1}H NMR ($CDCl_3$) δ 3.80 (3 H, s), 3.83 (3 H, s), 4.11 (2 H, d, J = 4.4), 6.29 (1 H, brs), 7.09 (1 H, t, J = 8.0), 7.40–7.80 (10 H, m), 8.19 (1 H, d, J = 7.6); IR (KBr) 3325, 2210, 1725, 1690 cm^{-1}. Anal. ($C_{24}H_{21}N_3O_4$) C, H, N.

Methyl 1-[(2'-Cyanobiphenyl-4-yl)methyl]-2,3-dihydro-2-oxo-1*H*-benzimidazole-7-carboxylate (15). A mixture of **14** (10.5 g, 25.3 mmol) and NaOMe (28% in MeOH; 10.1 g, 51.8 mmol) in MeOH (100 mL) was refluxed for 21 h. The reaction mixture was adjusted to pH 3–4 with 1 N HCl, diluted with water, and extracted with $CHCl_3$. The extract was washed with water and dried (Na_2SO_4). After evaporation of the solvent, the residue was recrystallized from $CHCl_3$–MeOH to give **15** (8.7 g, 89%) as colorless needles: mp 250–253 °C; ^{1}H NMR (DMSO-d_6) δ 3.65 (3 H, s), 5.35 (2 H, s), 7.04–7.16 (3 H, m), 7.24–7.28 (2 H, m), 7.48–7.59 (4 H, m), 7.76 (1 H, dt, J = 1.4 and 7.7), 7.92 (1 H, dd, J = 1.3 and 7.9); IR (KBr) 2210, 1720, 1690, 1635 cm^{-1}. Anal. ($C_{23}H_{17}N_3O_3 \cdot 0.3H_2O$) C, H, N.

Methyl 2-Chloro-1-[(2'-cyanobiphenyl-4-yl)methyl]-1*H*-benzimidazole-7-carboxylate (16). A mixture of **15** (8.0 g, 21 mmol) and phosphorus oxychloride (30 mL) was refluxed for 8 h, and then the reaction mixture was concentrated in vacuo. The residue was poured into ice–water and extracted with $CHCl_3$. The extract was washed with water and dried (Na_2SO_4). The

Table VI. Physicochemical Data of 1-[[2'-(1*H*-Tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-benzimidazolecarboxylates



compd	R	R^2	synthetic method[a]	% yield	recryst solvent[b]	mp, °C	formula[c]
17a	Me	Et	F	49	A	204.5–206	$C_{25}H_{22}N_6O_2 \cdot 0.4H_2O$
17b	Et	Et	F	40	A	188–189	$C_{26}H_{24}N_6O_2 \cdot 0.4H_2O$
17d	*i*-Pr	Et	F	52	A	144–146	$C_{27}H_{20}N_6O_2 \cdot 0.25EtOAc \cdot H_2O$
17e	c-Pr	Me	G	70	C	189–190	$C_{26}H_{22}N_6O_2 \cdot 0.3EtOAc$
17f	*s*-Bu	Et	F	43	B	128–130	$C_{28}H_{20}N_6O_2 \cdot 0.4EtOAc \cdot 0.4H_2O$
17g	*i*-Bu	Et	F	71	B	197–198	$C_{28}H_{20}N_6O_2$
18a	$MeOCH_2$	Me	G	68	G	191–194	$C_{25}H_{22}N_6O_3 \cdot 0.6H_2O$
18b	$EtOCH_2$	Me	G	61	G	214–217	$C_{26}H_{24}N_6O_3 \cdot 0.2H_2O$
18c	$MeSCH_2$	Me	G	56	G	186–188	$C_{25}H_{22}N_6O_2 \cdot 0.5H_2O$
18d	$EtSCH_2$	Et	G	75		amorphous[d]	
18e	$MeOCH_2CH_2$	Me	G	35		amorphous	$C_{26}H_{24}N_6O_3 \cdot 0.3H_2O$
18f	$MeSCH_2CH_2$	Me	G	16		amorphous	$C_{26}H_{24}N_6O_2S \cdot 0.3H_2O$
18g	$HOCH_2$	Et	G	84		amorphous[d]	
19a	MeO	Me	G	65	B	165–166	$C_{24}H_{20}N_6O_3 \cdot 0.1H_2O$
19b	EtO	Me	G	quant.	C	191–193	$C_{25}H_{22}N_6O_3 \cdot 0.2H_2O$
19c	PrO	Et	G	43	D	157–159	$C_{27}H_{20}N_6O_3$
19d	BuO	Me	G	91	D	146–148	$C_{27}H_{20}N_6O_3$
19e	allyl-O	Me	G	16	C	154–156	$C_{26}H_{22}N_6O_3 \cdot 0.5H_2O$
19f	CF_3CH_2O	Me	G	77	D	210–212	$C_{25}H_{19}F_3N_6O_3$
20	HS	Me	G	89	E	263–264 dec	$C_{24}H_{20}N_6O_2S \cdot 0.5H_2O$
21b	EtNH	Me	G	63	E	256–258	$C_{25}H_{23}N_7O_2 \cdot H_2O$
21c	PrNH	Et	G	76	C	170–173	$C_{27}H_{27}N_7O_2 \cdot 2H_2O$
21d	BuNH	Me	G	42	E	216–218	$C_{27}H_{27}N_7O_2 \cdot H_2O$
21e	EtN(Me)	Me	G	54	F	130–136	$C_{26}H_{25}N_7O_2 \cdot 0.6CHCl_3$
21f	morpholino	Me	G	62	F	163–167	$C_{27}H_{25}N_7O_3 \cdot 0.6H_2O$
21g	piperidino	Me	G	47	F	146–150	$C_{28}H_{27}N_7O_2 \cdot 0.8CHCl_3$
22a	MeS	Et	H	44	B	207–208 dec	$C_{25}H_{22}N_6O_2S$
22b	EtS	Et	H	57	D	153–154 dec	$C_{26}H_{24}N_6O_2S$
22c	PrS	Et	H	40	D	177–178 dec	$C_{27}H_{20}N_6O_2S$
22d	EtS	Me	I	90	D	177–178	$C_{25}H_{22}N_6O_2S \cdot 0.4H_2O$
34a[e]	EtO	Me	J	67	E	154–155	$C_{25}H_{22}N_6O_3 \cdot 0.2H_2O$
34b[f]	EtO	Me	J	60	E	155–157	$C_{25}H_{22}N_6O_3 \cdot 0.1i\text{-}PrO_2O$
34c[g]	EtO	Me	J	55	E	207–208	$C_{25}H_{22}N_6O_3 \cdot 0.3H_2O$

[a] Method F: NaN_3, NH_4Cl, DMF. Method G: (1) Me_3SnN_3, toluene, (2) 1 N HCl, MeOH. Method H: **16**, alkyl iodide, 1 N NaOH, MeOH. Method I: **17a** or **17b**, MeONa, MeOH. Method J: **33**, 1 N HCl. [b] A = EtOH; B = EtOAc; C = EtOAc–MeOH; D = EtOAc–hexane; E = $CHCl_3$–MeOH; F = *i*-Pr_2O–$CHCl_3$; G = *i*-Pr_2O–EtOAc. [c] All compounds gave satisfactory analyses (C, H, N). [d] The products were used without further purification. [e] Benzimidazole-4-carboxylate. [f] Benzimidazole-5-carboxylate. [g] Benzimidazole-6-carboxylate.

solvent was evaporated in vacuo and the residue was purified by flash column chromatography ($CHCl_3$ and then $CHCl_3$–MeOH = 10:1 to 5:1) to give **16** and recovery of **15** (2.2 g). The product was recrystallized from $CHCl_3$–MeOH to give **16** (2.9 g, 34%) as colorless needles: mp 154–157 °C; ^1H NMR ($CDCl_3$) δ 3.78 (3 H, s), 5.95 (2 H, s), 7.06 (2 H, d, J = 8.2), 7.31 (1 H, t, J = 8.0), 7.39–7.48 (4 H, m), 7.58–7.66 (1 H, m), 7.71–7.77 (2 H, m), 7.93 (1 H, dd, J = 1.2 and 8.0); IR (KBr) 2240, 1720 cm^{-1}. Anal. ($C_{28}H_{16}N_3ClO_2$) C, H, N.

Methyl 1-[(2'-Cyanobiphenyl-4-yl)methyl]-2-morpholino-1*H*-benzimidazole-7-carboxylate (13f). A mixture of **16** (0.8 g, 2.0 mmol) and morpholine (15 mL) was stirred at 100–120 °C for 2 h. The reaction mixture was concentrated in vacuo, diluted with water, and extracted with EtOAc. The extract was washed with water and dried (Na_2SO_4). After evaporation of the solvent, the residue was recrystallized from EtOAc–hexane to give **13f** (0.69 g, 77%) as colorless crystals: mp 165–166 °C; ^1H NMR ($CDCl_3$) δ 3.38 (4 H, t, J = 4.6), 3.72 (3 H, s), 3.90 (4 H, t, J = 4.7), 5.63 (2 H, s), 6.89 (2 H, d, J = 8.2), 7.20 (1 H, t, J = 7.9), 7.37–7.65 (6 H, m), 7.74 (1 H, dd, J = 1.5 and 7.9), 7.82 (1 H, dd, J = 1.1 and 7.9); IR (KBr) 2225, 1715 cm^{-1}. Anal. ($C_{27}H_{24}N_4O_3$) C, H, N.

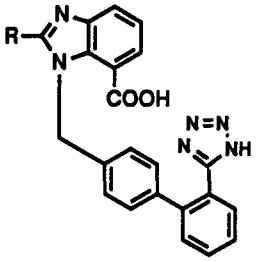
Methyl 1-[(2'-Cyanobiphenyl-4-yl)methyl]-2-piperidino-1*H*-benzimidazole-7-carboxylate (13g). Compound **13g** was obtained in 81% yield as colorless crystals: mp 119–121 °C (from toluene–hexane), from **16** and piperidine by a procedure similar to that used to prepare **13f**: ^1H NMR ($CDCl_3$) δ 1.62–1.77 (6 H, m), 3.31–3.36 (4 H, m), 3.73 (3 H, s), 5.58 (2 H, s), 6.88 (2 H, d, J = 8.4), 7.15 (1 H, t, J = 7.8), 7.35–7.49 (5 H, m), 7.56–7.64 (1 H, m), 7.73 (1 H, dd, J = 1.3 and 7.6), 7.79 (1 H, dd, J = 1.2 and 8.0); IR (KBr) 2225, 1720 cm^{-1}. Anal. ($C_{28}H_{26}N_4O_2 \cdot 0.1H_2O$) C, H, N.

Ethyl 2-Methyl-1-[[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-carboxylate (17a). A mixture of **7a** (2.5 g, 6.3 mmol), NaN_3 (3.9 g, 60 mmol), and NH_4Cl (3.2 g, 60 mmol) in DMF (30 mL) was stirred at 115 °C for 90 h. The reaction mixture was diluted with aqueous NH_4Cl and extracted with EtOAc. The extract was washed with water and dried ($MgSO_4$). The solvent was evaporated in vacuo and the residue was purified by column chromatography ($CHCl_3$–MeOH = 100:1 and then 5:1). The product was recrystallized from EtOH to give **17a** (1.4 g, 49%) as colorless prisms: mp 204.5–206 °C; ^1H NMR ($CDCl_3$–CF_3COOD) 1.27 (3 H, t), 2.90 (3 H, s), 4.30 (2 H, q), 5.93 (2 H, s), 6.93 (2 H, d), 7.10 (2 H, d), 7.40–7.80 (5 H, m), 8.00 (2 H, d); IR (Nujol) 1725 cm^{-1}. Anal. ($C_{25}H_{22}N_6O_2 \cdot 0.4H_2O$) C, H, N.

Compounds **17b,d,f,g** and **24c,h** were prepared by a procedure similar to that described above, and the results are shown in Tables VI and VII.

Methyl 2-Ethoxy-1-[[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-carboxylate (19b). A mixture of **9b** (52 g, 0.126 mol) and trimethyltin azide[14] (100 g, 9.49 mol)

Table VII. Physicochemical Data of 1-[[2′-(1*H*-Tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-benzimidazolecarboxylic Acids



compd	R	synthetic method[a]	% yield	recryst solvent[b]	mp, °C	formula[c]
24a	Me	K	60	A	283–284 dec	$C_{25}H_{18}N_6O_2 \cdot 0.2H_2O$
24b	Et	K	58	B	261–262 dec	$C_{24}H_{20}N_6O_2$
24c	Pr	F	22	B	275–276 dec	$C_{25}H_{22}N_6O_2 \cdot 0.5H_2O$
24d	*i*-Pr	K	71	B	265–267 dec	$C_{25}H_{22}N_6O_2 \cdot 0.3H_2O$
24e	c-Pr	K	73	C	259–260 dec	$C_{25}H_{20}N_6O_2 \cdot 0.5H_2O$
24f	*s*-Bu	K	79	D	184–186	$C_{26}H_{24}N_6O_2 \cdot 0.5H_2O$
24g	*i*-Bu	K	62	D	205–207 dec	$C_{26}H_{24}N_6O_2 \cdot 0.4H_2O$
24h	Pen	F	29	D	205.5–207 dec	$C_{27}H_{20}N_6O_2 \cdot 0.2H_2O$
25a	$MeOCH_2$	K	31	G	272–274	$C_{24}H_{20}N_6O_3$
25b	$EtOCH_2$	K	80	G	243–245	$C_{25}H_{22}N_6O_3 \cdot 0.5H_2O$
25c	$MeSCH_2$	K	82	H	270–272	$C_{24}H_{20}N_6O_2S \cdot 0.5H_2O$
25d	$EtSCH_2$	K	76	G	157–160	$C_{25}H_{22}N_6O_2S \cdot 0.9H_2O$
25e	$MeOCH_2CH_2$	K	71	H	>300	$C_{25}H_{22}N_6O_3 \cdot 0.5H_2O$
25f	$MeSCH_2CH_2$	K	61	H	244–248	$C_{25}H_{22}N_6O_2S$
25g	$MeNHCH_2$	K	48	H	>300	$C_{24}H_{21}N_7O_2 \cdot 0.5H_2O$
26a	MeO	K	77	C	208–209 dec	$C_{23}H_{18}N_6O_3 \cdot 0.7H_2O$
26b	EtO	K	85	C	180–181	$C_{24}H_{20}N_6O_3$
26c	PrO	K	69	E	174–175	$C_{25}H_{22}N_6O_3 \cdot 0.3H_2O$
26f	CF_3CH_2O	K	87	F	204–206	$C_{24}H_{17}F_3N_6O_3 \cdot H_2O$
27a	MeNH	M	40	C	247–250 dec	$C_{23}H_{18}N_7O_2 \cdot 2H_2O$
27b	EtNH	L	63	C	240–242 dec	$C_{24}H_{21}N_7O_2 \cdot 1.1H_2O$
27c	PrNH	L	73	C	244–246 dec	$C_{25}H_{23}N_7O_2 \cdot 0.5H_2O$
27d	BuNH	L	67	C	213–216 dec	$C_{26}H_{25}N_7O_2 \cdot H_2O$
27e	EtN(Me)	L	66	C	204–205 dec	$C_{25}H_{23}N_7O_2 \cdot 0.5H_2O$
27f	morpholino	L	59	C	202–206 dec	$C_{26}H_{25}N_7O_3 \cdot 0.6CHCl_3$
27g	piperidino	L	91	C	215–218 dec	$C_{27}H_{25}N_7O_2 \cdot 0.5CHCl_3$
28a	MeS	K	81	F	223–225 dec	$C_{23}H_{18}N_6O_2S \cdot 0.5EtOAc$
28b	EtS	K	64	E	209–210 dec	$C_{24}H_{20}N_6O_2S$
28c	PrS	K	91	F	222–223 dec	$C_{25}H_{22}N_6O_2S$
35a[d]	EtO	K	53	E	173–175	$C_{24}H_{20}N_6O_3$
35b[e]	EtO	K	82	C	207–208	$C_{24}H_{20}N_6O_3$
35c[f]	EtO	K	50	C	201–202	$C_{24}H_{20}N_6O_3$

[a] Method F: **7c** or **7h**, NaN_3, NH_4Cl, DMF. Method K: 1 N NaOH, MeOH. Method L: LiOH, H_2O–THF. Method M: (1) **13a**, Me_3SnN_3, toluene, (2) 1 N HCl, (3) 1 N NaOH, MeOH. [b] A = DMF–EtOH–H_2O; B = DMF–EtOH; C = $CHCl_3$–MeOH; D = EtOH; E = EtOAc–MeOH; F = EtOAc–hexane; G = DMF–MeOH–H_2O; H = DMF–H_2O. [c] All compounds gave satisfactory analyses (C, H, N). [d] Benzimidazole-4-carboxylic acid. [e] Benzimidazole-5-carboxylic acid. [f] Benzimidazole-6-carboxylic acid.

in toluene (500 mL) was refluxed for 29 h. While the reaction mixture was hot, the precipitate was collected by filtration and suspended in 1 N HCl (130 mL) and MeOH (100 mL). The mixture was stirred at room temperature for 15 min and then diluted with water. The precipitate was collected by filtration and purified by column chromatography ($CHCl_3$ and then $CHCl_3$–MeOH = 10:1). The product was recrystallized from $CHCl_3$–EtOAc to give **19b** (57 g, quant.) as colorless needles: mp 191–193 °C; ^1H NMR ($CDCl_3$) 1.43 (3 H, t, J = 7.0), 3.57 (3 H, s), 4.30 (2 H, q, J = 7.1), 5.54 (2 H, s), 6.72 (2 H, d, J = 8.2), 6.84–6.97 (4 H, m), 7.28–7.33 (1 H, m), 7.40 (1 H, dd, J = 1.8 and 7.0), 7.57–7.62 (2 H, m), 8.03–8.07 (1 H, m); IR (KBr) 1720, 1280, 1250, 1040 cm^{-1}. Anal. ($C_{25}H_{22}N_6O_3 \cdot 0.2H_2O$) C, H, N.

Compounds **18a–g**, **19a,c–f**, **20**, and **21a–g** were prepared by a procedure similar to that described above, and the results are shown in the Table VI.

Ethyl 2-(Methylthio)-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-carboxylate (22a). To a solution of **20** (0.68 g, 1.5 mmol) in 1 N NaOH (3.0 mL, 3.0 mmol) and EtOH (10 mL) was added dropwise iodomethane (0.24 g, 1.7 mmol) and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was adjusted to pH 3–4 and the precipitate was collected by filtration, which was purified by flash column chromatography ($CHCl_3$–MeOH = 10:1). The product was recrystallized from EtOAc to give **22a** (0.31 g, 44%) as colorless prisms: mp 207–208 °C dec; ^1H NMR (DMSO-d_6) δ 1.13 (3 H, t, J = 7.1), 2.77 (3 H, s), 4.14 (2 H, q, J = 7.1), 5.62 (2 H, s), 6.84 (2 H, d, J = 8.3), 7.02 (2 H, d, J = 8.3), 7.26 (1 H, t, J = 7.8), 7.46–7.70 (5 H, m), 7.85 (1 H, dd, J = 1.1 and 7.9); IR (KBr) 1705 cm^{-1}. Anal. ($C_{25}H_{22}N_6O_2S$) C, H, N.

Compounds **22b,c** were prepared by a procedure similar to that described above, and the results are shown in Table VI.

Methyl 2-(Ethylthio)-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-carboxylate (22d). A solution of **22b** (0.65 g, 1.3 mmol) and 4.9 M NaOMe (in MeOH; 0.8 mL, 3.9 mmol) in MeOH (15 mL) was stirred at room temperature for 17 h. The reaction mixture was concentrated in vacuo, diluted with water, and adjusted to pH 3–4 with 1 N HCl. The precipitate was collected by filtration and purified by flash column chromatography ($CHCl_3$–MeOH = 10:1). The product was recrystallized from EtOAc–hexane to give **22d** (0.56 g, 90%) as colorless prisms: mp 177–178 °C; ^1H NMR ($CDCl_3$) δ 1.39 (3 H, t, J = 7.4), 3.25 (2 H, q, J = 7.4), 3.71 (3 H, s), 5.66 (2 H, s), 6.80 (2 H, d, J = 8.5), 6.98 (2 H, d, J = 8.5), 7.11 (1 H, t, J = 7.9), 7.33–7.37 (1 H, m), 7.43–7.61 (4 H, m), 8.09–8.13 (1 H, m); IR (KBr) 1705 cm^{-1}. Anal. ($C_{25}H_{22}N_6O_2S \cdot 0.4H_2O$) C, H, N.

Methyl 2-(Ethylsulfinyl)-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-carboxylate (23). To an ice-cooled solution of **22d** (0.10 g, 0.21 mmol) in $CHCl_3$ (6 mL) was added dropwise a solution of *m*-CPBA (80%; 46 mg, 0.21 mmol) in $CHCl_3$ (2 mL). The reaction mixture was purified by flash column chromatography ($CHCl_3$ and then $CHCl_3$–MeOH = 10:1) and the product was recrystallized from EtOAc–hexane to give **23** (31 mg, 31%) as colorless needles: mp 176–178 °C dec;

^{1}H NMR ($CDCl_3$) δ 1.38 (3 H, t, J = 7.4), 3.40–3.59 (2 H, m), 3.82 (3 H, s), 5.95 (1 H, d, J = 16.4), 6.26 (1 H, d, J = 16.4), 6.88 (2 H, d, J = 8.0), 7.05 (2 H, d, J = 8.0), 7.35–7.60 (4 H, m), 7.84 (1 H, d, J = 7.6), 7.98–8.02 (2 H, m); IR (KBr) 1715, 1280, 1020 cm^{-1}. Anal. ($C_{25}H_{22}N_6O_3S$) C, H, N.

2-Ethoxy-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-carboxylic Acid (26b). A solution of **19b** (57 g, 125 mmol) and 1 N NaOH (380 mL, 375 mmol) in MeOH (190 mL) was stirred at 80–90 °C for 1 h. After MeOH was evaporated in vacuo, the residue was adjusted to pH 3–4 with concentrated HCl. The precipitate was collected by filtration and recrystallized from MeOH–$CHCl_3$ to give **26b** (47 g, 85%) as colorless needles: mp 180–181 °C; ^{1}H NMR (DMSO-d_6) δ 1.38 (3 H, t, J = 7.0), 4.58 (2 H, q, J = 7.0), 5.62 (2 H, s), 6.92 (2 H, d, J = 8.5), 7.01 (2 H, d, J = 8.5), 7.17 (1 H, t, J = 7.8), 7.47–7.69 (6 H, m); IR (KBr) 1710, 1610 cm^{-1}. Anal. ($C_{24}H_{20}N_6O_3$) C, H, N.

Compounds **24a,b,d–g**, **25a–g**, **26a,c,f**, **28a–c**, and **35a–c** were prepared by a procedure similar to that described above, and the results are shown in Table VII.

2-(Ethylamino)-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-carboxylic Acid (27b). A mixture of **21b** (0.52 g, 1.1 mmol) and lithium hydroxide monohydrate (0.18 g, 4.4 mmol) in THF–H_2O (5 mL: 5 mL) was stirred at 60 °C for 2 h. After THF was evaporated in vacuo, the residue was adjusted to pH 4–5 with 1 N HCl. The precipitate was collected by filtration and recrystallized from MeOH–$CHCl_3$ to give **27b** (0.30 g, 63%) as colorless crystals: mp 240–242 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.20 (3 H, t, J = 7.2), 3.43 (2 H, q, J = 7.2), 5.62 (2 H, s), 6.85 (2 H, d, J = 8.2), 6.99 (2 H, d, J = 8.0), 7.10 (1 H, t, J = 7.8), 7.34 (1 H, d, J = 6.8), 7.44–7.68 (5 H, m); IR (KBr) 1660 cm^{-1}. Anal. ($C_{24}H_{21}N_7O_2 \cdot 1.1H_2O$) C, H, N.

Compounds **27a,c–g** were prepared by a procedure similar to that described above, and the results are shown in Table VII.

Ethyl 2-(Chloromethyl)-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl)methyl]-1*H*-benzimidazole-7-carboxylate (29). Thionyl chloride (0.3 mL) was added dropwise to a solution of **18g** (0.2 g, 0.4 mmol) in CH_2Cl_2 (3 mL) and then the resulting solution was refluxed for 3 h. The reaction mixture was washed with water and concentrated in vacuo to dryness to give **29** (0.2 g, 96%) as a pale yellow amorphous powder: ^{1}H NMR ($CDCl_3$) δ 1.29 (3 H, t), 4.19 (2 H, q), 4.63 (2 H, s), 5.77 (2 H, s), 6.75 (2 H, d), 7.03 (2 H, d), 7.28 (1 H, t), 7.35–7.39 (1 H, m), 7.56–7.72 (4 H, m), 8.06–8.11 (1 H, m).

Ethyl 2-[(Methylamino)methyl]-1-[[2′-(1*H*-tetrazol-5-yl-)biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-carboxylate (30). A mixture of **29** (0.2 g, 0.4 mmol) and 40% methanol solution of methylamine (0.33 g, 4.2 mmol) in acetonitrile (5 mL) was stirred at 60 °C for 77 h. The reaction mixture was cooled to room temperature. The precipitate was collected by filtration and washed successively with CH_2Cl_2 and water to give **30** (0.12 g, 61%) as yellow prisms: ^{1}H NMR (DMSO-d_6) δ 1.14 (3 H, t), 2.62 (3 H, s), 4.16 (2 H, q), 4.39 (2 H, s), 5.71 (2 H, s), 6.73 (2 H, d), 7.03 (2 H, d), 7.27–7.46 (4 H, m), 7.54–7.63 (2 H, m), 7.94 (1 H, dd).

Methyl 2-Ethoxybenzimidazole-4-carboxylate (32a). A mixture of methyl 2,3-diaminobenzoate[8] (3.3 g, 20 mmol), tetraethoxymethane (4.2 g, 22 mmol), and acetic acid (1.2 g, 20 mmol) was stirred at 90–100 °C for 4 h. The reaction mixture was diluted with EtOAc, washed with water, and dried ($MgSO_4$). The solvent was evaporated in vacuo and the residue was purified by flash column chromatography (EtOAc–hexane = 1:3 and then 1:2). The product was recrystallized from EtOAc–hexane to give **32a** (1.6 g, 36%) as yellow plates: mp 135–136 °C; ^{1}H NMR ($CDCl_3$) δ 1.49 (3 H, t, J = 7.0), 3.98 (3 H, s), 4.62 (2 H, q, J = 7.0), 7.20 (1 H, t, J = 7.9), 7.69–7.76 (2 H, m), 9.50 (1 H, br); IR (KBr) 1690, 1620, 1260, 1200, 1190, 1145, 1030 cm^{-1}. Anal. ($C_{11}H_{12}N_2O_3$) C, H, N.

Methyl 2-Ethoxybenzimidazole-5-carboxylate (32b). Compound **32b** was prepared in 39% yield as colorless crystals: mp 171–172 °C (from EtOAc–MeOH) by a procedure similar to that used to prepare **32a**: ^{1}H NMR ($CDCl_3$) δ 1.47 (3 H, t, J = 7.2), 3.92 (3 H, s), 4.62 (2 H, q, J = 7.1), 7.40 (1 H, brs), 7.90 (1 H, dd, J = 1.5 and 8.5), 8.07 (1 H, brs); IR (KBr) 1730, 1715, 1225, 1085, 1065 cm^{-1}. Anal. ($C_{11}H_{12}N_2O_3$) C, H, N.

Methyl 2-Ethoxy-1-[[2′-[N-(triphenylmethyl)tetrazol-5-yl]biphenyl-4-yl]methyl]-1*H*-benzimidazole-4-carboxylate (33a) and -7-carboxylate (33d). To an ice-cooled solution of **32a** (0.44 g, 2.0 mmol) in DMF (2 mL) was added sodium hydride (60% in oil; 90 mg, 2.2 mmol) and the mixture was stirred at the same temperature for 15 min. 5-[4′-(Bromomethyl)biphenyl-2-yl]-1*H*-(*N*-triphenylmethyl)tetrazole[3b] (1.1 g, 2.0 mmol) was added to the reaction mixture and the reaction mixture was stirred at room temperature for 3 h. The resulting mixture was diluted with water and extracted with EtOAc. The extract was washed with water and dried ($MgSO_4$). After the solvent was evaporated in vacuo, the residue was purified by flash column chromatography (EtOAc–hexane = 1:2 and then 1:1). The first eluate was concentrated in vacuo and the product was recrystallized from EtOAc to give **33d** (0.25 g, 18%) as colorless prisms: mp 171–172 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.33 (3 H, t, J = 7.0), 3.60 (3 H, s), 4.56 (2 H, q, J = 7.0), 5.45 (2 H, s), 6.78 (2 H, d, J = 8.3), 6.85–6.91 (6 H, m), 6.98 (2 H, d, J = 8.3), 7.19 (1 H, t, J = 7.8), 7.26–7.46 (1 H, m), 7.48–7.64 (2 H, m), 7.69–7.79 (2 H, m); IR (KBr) 1720, 1610, 1275, 1245, 1210, 1120, 1035 cm^{-1}. Anal. ($C_{44}H_{36}N_6O_3 \cdot 0.3H_2O$) C, H, N. The second eluate was concentrated in vacuo and the product was recrystallized from EtOAc–$CHCl_3$ to give **33a** (0.67 g, 48%) as colorless prisms: mp 207–208 °C dec; ^{1}H NMR (DMSO-d_6) δ 1.37 (3 H, t, J = 7.0), 3.87 (3 H, s), 4.61 (2 H, q, J = 7.0), 5.22 (2 H, s), 6.82–6.88 (6 H, m), 7.02–7.12 (5 H, m), 7.25–7.64 (14 H, m), 7.79 (1 H, dd, J = 1.6 and 7.9); IR (KBr) 1700, 1615, 1285, 1240, 1125, 1050 cm^{-1}. Anal. ($C_{44}H_{36}N_6O_3 \cdot 0.3H_2O$) C, H, N.

Methyl 2-Ethoxy-1-[[2′-[*N*-(triphenylmethyl)tetrazol-5-yl]biphenyl-4-yl]methyl]-1*H*-benzimidazole-5-carboxylate (33b) and -6-carboxylate (33c). Compounds **33b,c** were prepared by a procedure similar to that used to prepare **33a**. The mixture was purified by column chromatography ($CHCl_3$–EtOAc = 20:1). The first eluate was concentrated in vacuo to give **33c** (31%) as colorless syrup: ^{1}H NMR ($CDCl_3$) δ 1.44 (3 H, t, J = 7.1), 3.85 (3 H, s), 4.63 (2 H, q, J = 7.1), 5.07 (2 H, s), 6.88–6.96 (7 H, m), 7.07 (2 H, d, J = 8.4), 7.18–7.35 (11 H, m), 7.43–7.49 (2 H, m), 7.56 (1 H, d, J = 8.6), 7.81 (1 H, d, J = 1.2), 7.89–7.95 (2 H, m); IR (neat) 1720, 1640, 1275, 1240, 1050 cm^{-1}. The second eluate was concentrated in vacuo to give **33b** (32%) as colorless syrup: ^{1}H NMR ($CDCl_3$) δ 1.45 (3 H, t, J = 7.1), 3.91 (3 H, s), 4.64 (2 H, q, J = 7.1), 5.07 (2 H, s), 6.87–6.98 (8 H, m), 7.08 (2 H, d, J = 8.4), 7.17–7.35 (11 H, m), 7.43–7.48 (2 H, m), 7.77 (1 H, dd, J = 1.5 and 8.3), 7.90–7.95 (1 H, m), 8.27 (1 H, d, J = 1.4); IR (neat) 1720, 1680, 1635, 1260, 1225, 1050 cm^{-1}.

Methyl 2-Ethoxy-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl-]methyl]-1*H*-benzimidazole-4-carboxylate (34a). A mixture of **33a** (0.67 g, 1.0 mmol) and 1 N HCl (2 mL) in MeOH–$CHCl_3$ (30 mL: 30 mL) was stirred at 0–5 °C for 4 h. After addition of 2 N NaOH (2 mL), the solvent was evaporated in vacuo. The precipitate was collected by filtration and purified by flash column chromatography ($CHCl_3$ and then $CHCl_3$–MeOH = 10:1). The product was recrystallized from $CHCl_3$–MeOH to give **34a** (0.31 g, 67%) as colorless needles: mp 154–155 °C; ^{1}H NMR ($CDCl_3$) δ 1.41 (3 H, t, J = 7.1), 3.86 (3 H, s), 4.63 (2 H, q, J = 7.1), 5.27 (2 H, s), 7.06 (2 H, d, J = 8.3), 7.16 (1 H, t, J = 8.0), 7.19 (2 H, d, J = 8.3), 7.49–7.66 (6 H, m); IR (KBr) 1712, 1618, 1290, 1244, 1217, 1140, 1059 cm^{-1}.

Compounds **34b,c** were prepared by a procedure similar to that described above, and the results are shown in Table VI.

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