Nonpeptide Angiotensin II Receptor Antagonists. Synthesis and Biological Activity of Potential Prodrugs of Benzimidazole-7-carboxylic Acids[1]

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In order to improve the oral bioavailability (BA) of 2-butyl-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-carboxylic acid (**3**: CV-11194) and 2-ethoxy-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-carboxylic acid (**4**: CV-11974), novel angiotensin II (AII) receptor antagonists, chemical modification to yield prodrugs has been examined. After selective tritylation of the tetrazole rings in **3** and **4**, treatment of N-tritylated benzimidazole-7-carboxylic acids (**6**, **7**) with a variety of alkyl halides, followed by deprotection with hydrochloric acid, afforded esters of **3** and **4**. Mainly 1-(acyloxy)alkyl esters and 1-[(alkoxycarbonyl)oxy]alkyl esters, double ester derivatives, were synthesized. Their inhibitory effect on AII-induced pressor response in rats and oral BA were investigated. (Pivaloyloxy)methyl and (±)-1-[[(cyclohexyloxy)-carbonyl]oxy]ethyl esters of **3** and **4** showed marked increases in oral bioavailability which significantly potentiated the inhibitory effect of the parent compounds on AII-induced pressor response. Among them, (±)-1-[[(cyclohexyloxy)carbonyl]oxy]ethyl 2-ethoxy-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-carboxylate (**10s**, TCV-116) was selected as a candidate for clinical evaluation.

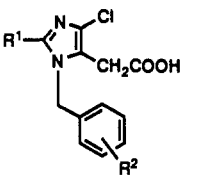
The renin–angiotensin system (RAS) plays an essential role in the regulation of blood pressure and seems to be critically involved in the development and maintenance of hypertension as well as congestive heart failure.[2] Angiotensin II (AII), an octapeptide produced from angiotensin I by the action of angiotensin converting enzyme localized on the endothelium of blood vessels in the lungs, kidneys, and many other organs, is the primary effector component of the RAS. AII is a powerful vasoconstrictor that exerts its action by interacting with specific receptors which are present on cell membranes. One of the possible modes of interrupting the RAS is AII receptor antagonism, and the discovery of nonpeptide AII antagonists, **1a** (CV-2973), **1b** (CV-2961),[3] and **2** (DuP 753: losartan)[4] (Chart I), has stimulated the recent development of new AII receptor antagonists.

In previous reports,[5] we have 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 (**3**, CV-11194)[5a] and 2-ethoxy-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-carboxylic acid (**4**, CV-11974)[5b] (Chart II) which are more potent and have a longer duration of action than **2**.

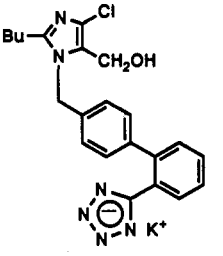
Although **3** and **4** are very potent AII antagonists, they were found to be absorbed rather inefficiently upon oral administration as indicated by the fact that much lower plasma concentrations were attained after oral administration as compared to parenteral administration. It is reasonable to assume that this is due to the highly polar character of these AII antagonists possessing two acidic groups, a carboxyl group and a tetrazole ring, and that a transient masking of these groups could improve oral absorption. Therefore, we investigated the possibility of improving the oral bioavailability (BA) of **3** and **4** by the prodrug approach, and here we describe the results.

Transient masking could be achieved by esterification of the carboxyl group, but preliminary experiments revealed that simple alkyl esters of **3** were hydrolyzed slowly in rat small intestine homogenate, rat plasma, and

Chart I

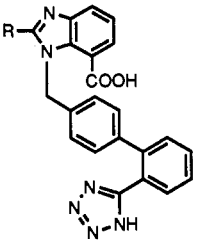


1a : R^1=Ph,R^2= 4'-OMe-3'-Me (CV-2973)
1b : R^1=Bu, R^2=2'-NO_2 (CV-2961)



2 (DuP 753, losartan)

Chart II



3: R=Bu (CV-11194)
4: R=EtO (CV-11974)

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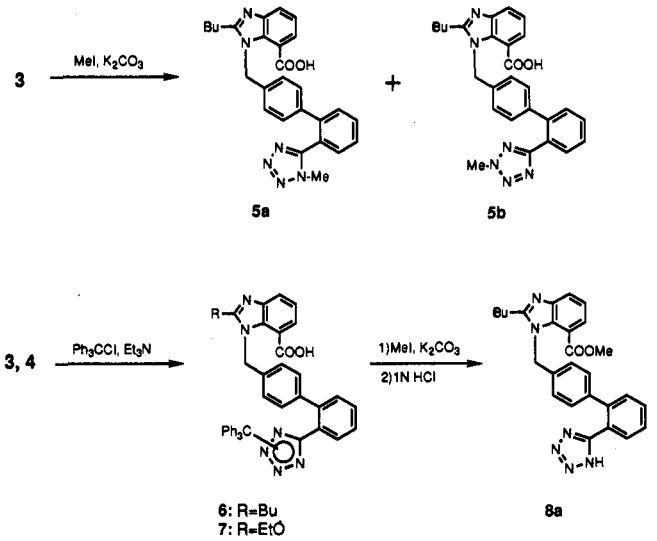
Scheme I



rat liver homogenate, indicating that a special type of ester would be needed to fulfill the requirement of rapid hydrolysis during passage into the blood stream. Well-known ester prodrugs formed by esterification of a carboxyl group are (acyloxy)methyl esters and [(alkoxycarbonyl)-oxy]methyl esters, double ester types, frequently utilized in the field of β-lactam antibiotics to improve oral absorption.[6] Double esters are hydrolyzed rapidly in the blood and tissues of several animal species and humans. Hydrolysis of a double ester is thought to proceed *via* a chemically unstable 1-hydroxyalkyl ester which rapidly collapses to the parent compound and the aldehyde. Since an *N*-(1-hydroxyalkyl)tetrazole also seems to be chemically unstable enough to regenerate the parent tetrazole, the tetrazole rings of **3** and **4** can also be used in prodrug synthesis.

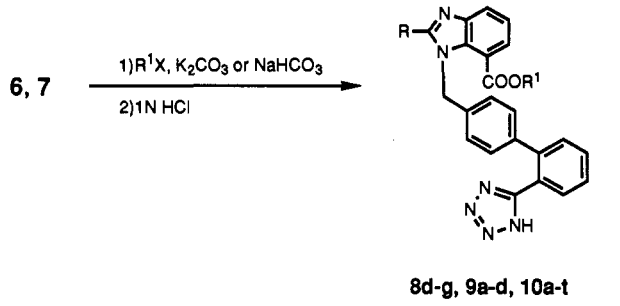
As an alternative to finding suitable enzymatically labile esters for acidic drugs, chemically labile esters have also been examined. In this respect, the principle of "neighboring group participation" or intramolecularly assisted cleavage has been an excellent source of ideas for prodrug design.[7] We have studied the use of disubstituted aminoalkyl esters and a hydroxyalkyl ester of **3** in an effort to improve oral absorption.

Chemistry

The compounds prepared for this study are shown in Tables I and III, and synthetic methods are outlined in Schemes I–III.

Direct alkylation of **3** or **4** with alkyl halides seemed to be the most convenient route to obtain a variety of esters. Since these compounds have three possible positions for alkylation, the carboxyl group and positions N-1 and N-2 in the tetrazole ring, we first examined regioselective methylation of **3** to obtain its methyl ester (**8a**). Methylation with equimolar amounts of methyl iodide in dimethylformamide (DMF) under ice-cooling and using potassium carbonate as a base gave *N*-methyltetrazoles (**5a**, **5b**), which were separated by flash column chromatography to afford the 1-methyl isomer (**5a**) in 52% yield and the 2-methyl isomer (**5b**) in 17% yield (Scheme I). Their structures were assigned based on the fact that in ^{13}C NMR spectra the carbons at the 5-position of the tetrazole rings in **5a** and **5b** appeared at δ 154.32 and δ 164.24, respectively, which are in accord with data reported

Scheme II



for 1- and 2-methyl-5-phenyltetrazole (δ 154.2 and δ 164.25, respectively).[8] Furthermore, this assignment was supported by the fact that the carbon of the *N*-methyl group in **5a** appeared upfield (δ 33.37) from that in **5b** (δ 39.20). Similar tendency was reported for 1- and 2-methyl-5-phenyltetrazole (δ 34.95 and δ 39.7, respectively).[9]

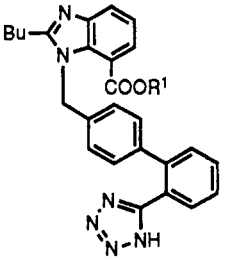
Although selective alkylation of the carboxyl group failed, these results suggested the possibility of selective protection of the tetrazole ring. We chose a trityl group as the protecting group for the tetrazole ring, since this protecting group can be removed at the appropriate time by mild acid treatment. Tritylation of **3** with trityl chloride under ice-cooling in the presence of triethylamine gave an *N*-trityltetrazole (**6**), whose alkylated position was not determined, in high yield. Methylation of **6** with methyl iodide followed by deprotection with 1 N HCl furnished a monomethylated product which was identified as the methyl ester (**8a**) produced by acid-catalyzed esterification of **3**.[5a] Using this method, a variety of esters of **3** and **4** were synthesized from *N*-trityltetrazoles (**6**, **7**) and alkyl halides[10] as shown in Scheme II and Table I.

Monoalkylation of **3** with iodomethyl pivalate[10f] afforded N-alkylated products (**11a**, **11b**) as an inseparable regioisomer mixture whose ratio was estimated from the integration of the methylene groups (δ 5.39 and δ 6.36) of the (pivaloyloxy)methyl groups in the ^1H NMR spectrum of the mixture as being about 3:1. The assignment of methylene groups was deduced from chemical shifts of the *N*-methyl groups in **5a** and **5b** (δ 3.15 and δ 4.21, respectively). The compounds whose carboxyl groups and tetrazole rings were masked (**12a**, **12b**) were prepared similarly by reacting **3** with 3.6 equiv of 4-(bromomethyl)-5-methyl-2-oxo-1,3-dioxolene[10e] as an inseparable regioisomer mixture (Scheme III). The ratio was estimated from the integration of the methylene groups (δ 4.54 and δ 5.41) of the (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl groups in the ^1H NMR spectrum of the mixture as being about 3:2.

Results and Discussion

Initially, analogues of **3** were evaluated *in vivo* for inhibitory effect on the pressor response induced by AII (100 ng/kg, iv) in conscious rats, and the results are listed in Table I.[11] Enhancement of the inhibitory activity was observed for double esters (**9a–d**), whereas simple alkyl (methyl, ethyl, butyl) esters (**8a–c**),[5a] 2-aminoethyl esters (**8e–g**), hydroxyethyl esters (**8h**), and N-alkylated tetrazole analogues (**5a**, **5b**, **11a,b**) showed activity comparable to or less than **3**. Masking of the tetrazole ring slightly improved the activity (**11a**, **11b** vs **3**), but additional masking of the tetrazole ring in **9d** failed to increase the activity (**9d** vs **12a**, **12b**). These results suggest that masking the carboxyl group is preferable to masking the

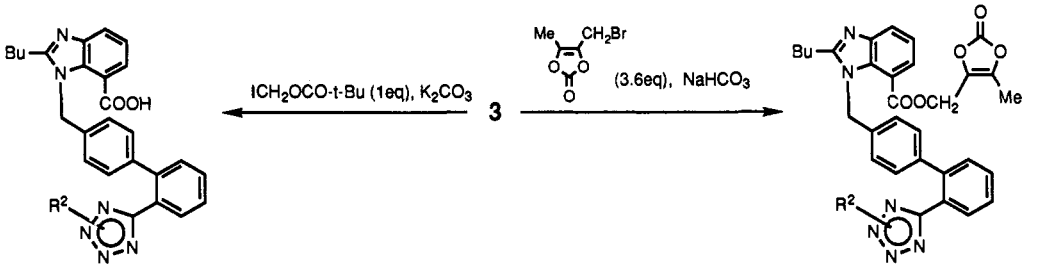
Table I. Inhibitory Effects of Analogues of **3** on AII-Induced Pressor Response and Bioavailabilities (BA) in Rats



compd	R^1	dose, mg/kg po	% inhibition[a] at time, h							BA,[b] %
			0.5	1	2	3	5	7	24	
3 (CD-11194)	H	1	8	33	45	49	55	53	42	5.7
8a	Me	1	11	52	50	47	38	27	11	10.9
8b	Et	3	7	25	46	51	68	63	47	2.4
8c	Bu	30	16	40	80	78	88	90	76	0.4
8d	CH_2(4-pyridyl)	3	4	16	18	16	18	8	NT[c]	0.6
8e	$CH_2CH_2NMe_2$	1	0	19	27	32	26	14	9	NT
8f	CH_2CH_2(morpholino)	10	67	94	96	96	96	96	66	NT
8g	CH_2CH_2(piperidino)	1	20	47	46	69	62	49	28	NT
8h	CH_2CH_2OH	1	7	7	10	11	21	25	20	0.5
9a	CH_2OCO-*t*-Bu	1	58	90	96	95	92	86	50	52.8
9b	CH(Me)OCOOEt	1	64	89	84	89	81	75	61	NT
9c	CH(Me)OCOO-*c*-hexyl	1	58	85	84	81	78	79	47	60.8
9d	CH_2(MD)[d]	1	32	63	81	88	75	77	55	NT
5a	H (1-Me)[e]	1	12	29	29	56	59	53	16	7.3
5b	H (2-Me)[e]	1	22	26	6	9	13	26	23	NT
11a, 11b[f]	H (1-, 2-CH_2OCO-*t*-Bu)[e]	1	7	4	33	63	67	69	32	NT
12a, 12b[g]	CH_2(MD)[d] (CH_2(MD)[d])[e]	1	7	9	33	60	59	46	17	NT
2 (DuP 753)		1	5	1	12	21	35	34	17	NT

[a] Percent inhibition of the AII (100 ng/kg iv)-induced pressor response at each time after administration of the test compounds in conscious male Sprague-Dawley rats ($n = 2$). The inhibition of the pressor response to AII was calculated from duplicate experiments except **2** (DuP 753) ($n = 4$). The inhibitory effect (percent inhibition) may vary less than 30%. The data in Figure 1 are indicative of the variation measured throughout this study. [b] Bioavailability was calculated from the ratio of the area under the plasma concentration–time curve (AUC) for 0 to infinity after oral dosing (10 mg/kg equivalent to **3**) of the test compounds to that after intravenous administration of **3** at a dose of 1 mg/kg in rats ($n = 3$). The following equation was used for the calculation: $BA = (AUC_{po}/AUC_{iv}) \times (dose_{iv}/dose_{po}) \times 100$. [c] NT means "not tested". [d] MD means "5-Methyl-2-oxo-1,3-dioxolen-4-yl". [e] Substituents on the tetrazole ring. [f] A mixture of the regioisomers (**11a**/**11b** = 3:1) was used. [g] A mixture of the regioisomers (**12a**/**12b** = 3:2) was used.

Scheme III



11a: R^2=1-t-BuCOOCH$_2$
11b: R^2=2-t-BuCOOCH$_2$

12a: R^2=1-(5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl
12b: R^2=2-(5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl

tetrazole ring. We examined some of these compounds in BA experiments in rats, assessing as **3** (Table I), and determined the rate of hydrolysis to **3** *in vitro* using 1% rat small intestine homogenate, 10% rat plasma, and 2% rat liver homogenate at 37 °C (Table II). The BA as **3** was increased by about 10-fold for double esters (**9a**, **9c**), which had a rapid onset of action. The BA as **3** after administration of the 1-methyltetrazole analogue (**5a**) was slightly improved, but that of the simple alkyl esters (**8b**, **8c**) was lower than that of **3**. The BA as **3** of the simple alkyl esters was decreased by increasing alkyl chain length in R^1. Although the methyl ester (**8a**) has a BA of ca. 30%, its BA as **3** was only 10.9%. These results indicate that the esterification of the carboxyl group in **3** results in an improvement of the oral BA by increasing the lipophilicity and the absence of a negative charge due to the carboxyl group during transport across the gut lumen. The low BA as **3** seen with **8a** and **8c** could be explained by their high resistance to enzymatic hydrolysis. No amount of **3** was detected after incubating **8a** and **8c** in the tissue homogenate for 60 min. The stability seemed to be ascribed to steric hindrance around the ester groups in these molecules. The compounds bearing a (pivaloyloxy)methyl group at the carboxyl group (**9a**) or the tetrazole ring (mixture of **11a** and **11b**) were hydrolyzed to **3** with a half-life ($t_{1/2}$) of 1.08 and 22.7 min, respectively, in 1% small intestine homogenate. In 10% plasma and 2% liver homogenate, **9a** and **11a,b** were also hydrolyzed rapidly to **3**, but the

Table II. Half-Lives ($t_{1/2}$) of Analogues of 3 and 4 in 1% Rat Small Intestine Homogenate, 2% Rat Liver Homogenate, or 10% Rat Plasma at 37 °C[a]

compd	tissue	$t_{1/2}$, min mean ± SD, n = 3
8a	1% SI[b]	stable[c]
	10% plasma	stable
	2% liver	stable
8c	1% SI	stable
8d	1% SI	stable
9a	1% SI	1.08 ± 0.06
	10% plasma	0.69 ± 0.01
	2% liver	3.61 ± 0.23
11a, 11b[d]	1% SI	22.7 ± 1.0
	10% plasma	3.94 ± 0.32
	2% liver	9.80 ± 0.19
10e	1% SI	0.30 ± 0.01
	10% plasma	0.15 ± 0.00
	2% liver	0.48 ± 0.01
10s	1% SI	4.92 ± 0.41
	10% plasma	2.73 ± 0.15
	2% liver	2.29 ± 0.06

[a] Final concentration was 10 μg/mL. Half-lives ($t_{1/2}$) were calculated from the concentration change of the analogues. [b] Rat small intestine homogenate. [c] 3 was not detected at 60 min after incubation. [d] A mixture of the regioisomers (11a/11b = 3:1) was used.

hydrolysis rate of **9a** was faster than that of **11a,b**. The difference in hydrolysis rate was reflected in their BA and their inhibitory effect on the pressor response induced by AII. These results proved double esters to be efficient prodrugs for **3**.

The goal of this research project was to find an optimal promoiety for **4** which is a more potent AII receptor antagonist than **3**. We applied the "double ester" prodrug technique to **4** as in the case of **3**. The inhibitory effect of **4** and its analogues on AII-induced pressor response in conscious rats and the BA as **4** after administration of these compounds were determined, and the results are shown in Table III. Although faster onset of the inhibitory effect after administration of the (acetyloxy)methyl ester (**10a**), (propionyloxy)methyl ester (**10b**), (butyryloxy)-methyl ester (**10c**), and (isovaleryloxy)methyl ester (**10d**) was observed, BA as **4** after administration of these esters was slightly lower than after administration of **4**. The [(cyclohexylcarbonyl)oxy]methyl ester (**10g**) and (benzoyloxy)methyl ester (**10h**) had an inhibitory effect, but the onset of action was slow. The inhibitory effect was significantly greater with 1-[[(alkyloxy)carbonyl]oxy]ethyl esters (**10o–s**), whereas it was only slightly greater with [[(alkyloxy)carbonyl]oxy]methyl esters (**10k–n**). Among the double esters, the (pivaloyloxy)methyl ester (**10e**) and (±)-1-[[(cyclohexyloxy)carbonyl]oxy]ethyl ester (**10s**) showed a pronounced inhibitory effect profile, fast onset and prolonged duration of action, and higher BA as **4** which was 7 times that of **4**. These esters (**10e**, **10s**) were hydrolyzed to **4** with a $t_{1/2}$ of 0.30 and 4.92 min, respectively, in 1% small intestine homogenate (Table II).

The (±)-1-[[(cyclohexyloxy)carbonyl]oxy]ethyl ester (**10s**) was selected as a candidate for clinical evaluation under the code name TCV-116, since adverse effects of the promoiety (pivalic acid) of **10e** have been reported.[12] As shown in Figure 1, the inhibitory effects of **10s** at 0.3 and 0.03 mg/kg po were more potent and long lasting than those of the parent compound (**4**). After oral administration of **10s** to rats at a dose of 1 mg/kg, **10s** was not detected in the plasma. In isolated rabbit aortic strips, **10s** and **4** inhibited AII (10^{-8} M)-induced contraction with IC_{50} values of 2.0×10^{-8} M and 2.0×10^{-10} M,[5b] respectively.[11] These results indicate that **10s** is rapidly transformed into **4** after the oral administration and then acts as a potent AII antagonist in the body.

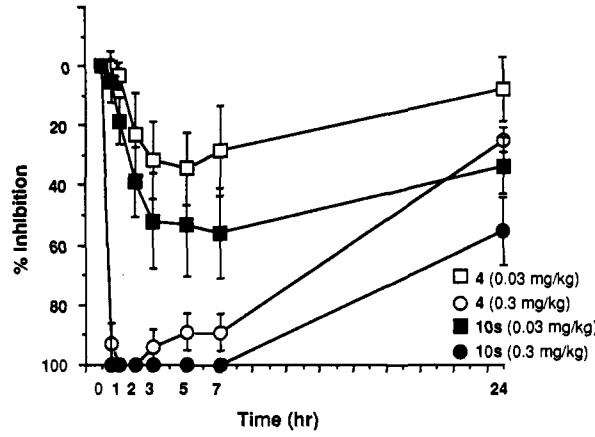


Figure 1. Inhibitory effects of **10s** (TCV-116) and **4** (0.03 and 0.3 mg/kg po) on AII (100 ng/kg iv)-induced pressor response in conscious normotensive rats (n = 4–5).

Conclusion

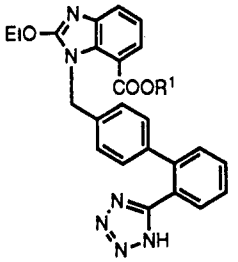
We successfully performed chemical modification of novel AII receptor antagonists, **3** and **4**, to improve oral absorption. Although simple alkyl esters (**8a–c**) and β-substituted ethyl esters (**8e–h**) did not have improved BA as **3** or increased AII antagonistic potency, double esters were found to be effective prodrugs of **3** and **4**. Among them, the (pivaloyloxy)methyl ester (**10e**) and (±)-1-[[(cyclohexyloxy)carbonyl]oxy]ethyl ester (**10s**) of **4** showed significantly enhanced BA as **4** and AII antagonistic potency. On the basis of its profile, **10s** has been selected for clinical evaluation as an antihypertensive agent and is the first example of applying the double ester prodrug technique to an orally effective AII antagonistic agent. We think that this double ester prodrug technique is synthetically easy for good overall yield from diacidic parent compounds and can be used with other diacidic nonpeptide AII antagonists[13] to increase their oral absorption. Further detailed studies on **10s** are in progress, and the results will be reported elsewhere.[14]

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 (^{1}H NMR) spectra were recorded on a Varian Gemini-200 (200 MHz) spectrometer. The carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a JEOL JNM-GX270 (67.8 MHz). 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 previously described.[5]

2-Butyl-1-[[2′-(1-(and 2-)methyltetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-carboxylic Acid (5a, 5b). To an ice-cooled mixture of **3** (0.94 g, 2.0 mmol) and potassium carbonate (0.28 g, 2.0 mmol) in DMF (6 mL) was added dropwise a solution of methyl iodide (0.28 g, 2.0 mmol) in DMF (2 mL), and the resulting mixture was stirred at that temperature for 20 min. The reaction mixture 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 ($CHCl_3$/MeOH = 10:1). The first eluent was concentrated in vacuo, and the product was recrystallized from EtOAc–$CHCl_3$ to give **5b** (0.16 g, 17%)

Table III. Inhibitory Effects of Analogues of **4** on AII-Induced Pressor Response and Bioavailabilities (BA) in Rats



compd	R^1	% inhibition[a] at time, h							BA,[b] %
		0.5	1	2	3	5	7	24	
4 (CV-11974)	H	7	24	51	67	85	91	43	5.0
10a	CH_2OCOMe	66	84	79	78	72	59	23	4.1
10b	CH_2OCOEt	76	76	60	60	38	31	−4	4.3
10c	CH_2OCOPr	100	84	78	67	54	48	6	3.5
10d	CH_2OCO-*i*-Pr	80	40	56	52	44	20	6	2.7
10e	CH_2OCO-*t*-Bu	42	77	88	86	87	86	43	34.9
10f	CH_2OCO-c-Pen	7	31	61	65	62	54	9	NT[c]
10g	CH_2OCO-c-hexyl	0	5	76	85	89	80	14	NT
10h	CH_2OCOPh	−4	−2	23	56	67	76	6	NT
10i	$CH_2OCOCH{=}CHPh$[d]	−3	36	80	80	61	64	3	NT
10j	CH(Me)OCOMe	86	90	92	86	84	75	28	8.8
10k	CH_2OCOO-*i*-Pr	23	55	79	72	68	57	28	NT
10l	$CH_2OCOOCH_2$-c-Pr	10	49	57	58	44	30	22	NT
10m	CH_2OCOO-c-Pen	5	14	55	68	77	64	14	NT
10n	CH_2OCOO-c-hexyl	1	−3	4	15	53	54	11	NT
10o	CH(Me)OCOOEt	74	87	95	89	81	71	7	4.8
10p	CH(Me)OCOO-*i*-Pr	70	91	84	79	80	67	12	NT
10q	$CH(Me)OCOOCHEt_2$	16	72	86	84	63	53	13	8.0
10r	CH(Me)OCOO-c-Bu	35	77	86	83	79	60	25	10.8
10s	CH(Me)OCOO-c-hexyl	38	76	80	87	82	75	36	33.4
10t	CH_2(MD)[e]	49	83	87	85	70	44	6	9.1

[a] Percent inhibition of the AII (100 ng/kg iv)-induced pressor response at each time after administration of the test compounds at dose of 0.1 mg/kg po in conscious male Sprague-Dawley rats ($n = 2$). The inhibition of the pressor response to AII was calculated from duplicate experiments except **4** and **10s** ($n = 3$). The inhibitory effect (percent inhibition) may vary less than 30%. The data in Figure 1 are indicative of the variation measured throughout this study. [b] Bioavailability was calculated from the ratio of the area under plasma concentration–time curve (AUC) for infinity after oral dosing (1 mg/kg equivalent to **4**) of the test compounds to that after intravenous administration of **4** at the same dose in rats ($n = 3$). [c] NT means "not tested". [d] Geometry of the double bond is trans. [e] MD means "5-methyl-2-oxo-1,3-dioxolen-4-yl".

as colorless needles: mp 226–228 °C dec; ^{1}H NMR ($CDCl_3$) δ 0.94 (3H, t, $J = 7.2$), 1.38–1.56 (2H, m), 1.79–1.94 (2H, m), 3.07 (2H, t, $J = 7.5$), 4.22 (3H, s), 5.84 (2H, s), 6.81 (2H, d, $J = 8.1$), 7.06 (2H, d, $J = 8.1$), 7.25–7.55 (4H, m), 7.74 (1H, d, $J = 7.6$), 7.81 (1H, dd, $J = 2.2$ and 6.8), 8.00 (1H, d, $J = 7.6$); ^{13}C NMR (DMSO-d_6) δ 13.52, 21.68, 26.29, 28.59, 39.20, 47.88, 118.36, 121.74 (two peaks were overlapped), 125.26, 125.59, 125.75, 127.65, 129.10, 130.15, 130.18, 130.59, 131.52, 135.76, 139.17, 140.75, 141.37, 157.22, 164.24, 167.31; IR (KBr) 1700 cm^{-1}. Anal. ($C_{27}H_{26}N_6O_2 \cdot 0.7H_2O$) C, H, N. The second eluent was concentrated in vacuo, and the product was recrystallized from EtOAc to give **5a** (0.49 g, 52%) as colorless prisms: mp 213–214 °C; ^{1}H NMR ($CDCl_3$) δ 0.95 (3H, t, $J = 7.4$), 1.38–1.57 (2H, m), 1.80–1.95 (2H, m), 2.99 (2H, t, $J = 8.0$), 3.18 (3H, s), 5.82 (2H, s), 6.80 (2H, d, $J = 8.2$), 6.97 (2H, d, $J = 8.2$), 7.27 (1H, t, $J = 7.7$), 7.48–7.68 (4H, m), 7.80 (1H, d, $J = 7.6$), 7.98 (1H, d, $J = 7.6$); ^{13}C NMR (DMSO-d_6) δ 13.55, 21.69, 26.49, 28.71, 33.37, 47.57, 117.82, 120.96, 122.07, 122.55, 124.74, 126.10, 127.87, 128.48, 130.16, 131.12, 131.60, 132.18, 137.30, 137.51, 140.83, 143.41, 154.32, 157.36, 167.50; IR (KBr) 1700 cm^{-1}. Anal. ($C_{27}H_{26}N_6O_2 \cdot 0.5H_2O$) C, H, N.

2-Butyl-1-[[2′-[1-(and 2-)[(pivaloyloxy)methyl]tetrazol-5-yl]biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-carboxylic Acid (11a, 11b). The mixture of **11a** and **11b** (3:1) was obtained by a procedure similar to that described above in 23% yield as colorless powder (from acetone–hexane): mp 188–191 °C dec; ^{1}H NMR ($CDCl_3$) δ 0.94 (3H, t, $J = 7.4$), 0.96 and 1.18 (9H, 2s), 1.36–1.55 (2H, m), 1.77–1.93 (2H, m), 2.90–2.97 (2H, m), 5.39 and 6.36 (2H, 2 s, 3:1 ratio), 5.81 (2H, s) 6.76–6.83 (2H, m), 6.96–7.03 (2H, m), 7.20–7.29 (1H, m), 7.38–7.97 (6H, m); IR (KBr) 1760, 1600 cm^{-1}. Anal. ($C_{32}H_{34}N_6O_4 \cdot 0.6H_2O$) C, H; N: calcd, 14.55; found, 14.13.

(5-Methyl-2-oxo-1,3-dioxolen-4-yl)methyl 2-Butyl-1-[[2′-[1-(and 2-)[(5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl]tetrazol-5-yl]biphenyl]methyl]-1*H*-benzimidazole-7-carboxylate (12a, 12b). The mixture of **12a** and **12b** (4:3) was obtained by a procedure similar to that described for **5a** and **5b**, except using 3.6 mol equiv of 4-(bromomethyl)-5-methyl-2-oxo-1,3-dioxolene,[10e] in 32% yield as pale brown amorphous powder: mp 68–71 °C; ^{1}H NMR ($CDCl_3$) δ 0.96 (3H, t, $J = 7.3$), 1.38–1.57 (2H, m), 1.80–2.20 (8H, m), 2.87–2.98 (2H, m), 4.54 (1.2H, s), 4.86 and 4.89 (2H, 2s), 5.41 (0.8H, s), 5.71 and 5.76 (2H, 2s), 6.72–6.77 (2H, m), 7.03 (2H, d, $J = 8.2$), 7.21–7.84 (6H, m), 7.97 (1H, d, $J = 8.0$); IR (KBr) 1820, 1735, 1720 cm^{-1}. Anal. ($C_{36}H_{32}N_6O_5 \cdot 0.5H_2O$), C, H, N.

2-Ethoxy-1-[[2′-[N-(triphenylmethyl)-1*H*-tetrazol-5-yl]-biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-carboxylic Acid (7). To an ice-cooled solution of **4** (29.0 g, 66.0 mmol) and triethylamine (7.33 g, 72.4 mmol) in CH_2Cl_2 (300 mL) was added dropwise a solution of trityl chloride (19.9 g, 71.4 mmol) in CH_2Cl_2 (80 mL), and the resulting mixture was stirred at that temperature for 1 h. The reaction mixture was washed with water and dried ($MgSO_4$). After evaporation of the solvent, the residue was purified by flash column chromatography ($CHCl_3$/MeOH = 40:1). The product was recrystallized from EtOAc–hexane to give **7** (76%) as colorless needles: mp 168–170 °C; ^{1}H NMR ($CDCl_3$) δ 1.40 (3H, t, $J = 7.1$), 4.61 (2H, q, $J = 7.1$), 5.58 (2H, s), 6.76 (2H, d, $J = 8.0$), 6.91–6.96 (8H, m), 7.12 (1H, t, $J = 7.9$), 7.17–7.41 (12H, m), 7.60 (1H, dd, $J = 1.2$ and 7.8), 7.73–7.82 (2H, m); IR (KBr) 1700 cm^{-1}. Anal. ($C_{43}H_{34}N_6O_3$) C, H, N.

2-Butyl-1-[2′-[N-(triphenylmethyl)-1*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-carboxylic Acid (6). Compound **6** was prepared, by a similar procedure to that described above, in 76% yield as colorless needles (from EtOAc–$CHCl_3$): mp 185–187 °C dec; ^{1}H NMR ($CDCl_3$) δ 0.91 (3H, t, $J = 7.2$), 1.30–1.48 (2H, m), 1.72–1.90 (2H, m), 2.84 (2H, t, $J = 7.9$), 5.72 (2H, s), 6.64 (2H, d, $J = 8.0$), 6.95–7.00 (8H, m), 7.11–7.46 (13H, m), 7.65 (1H, d, $J = 1.2$ and 7.6), 7.79–7.83 (1H,

Table IV. Physicochemical Data of Analogues

compd	X[a]	yield, %	recryst solvent[b]	mp, °C	formula[c]
8d	Cl	85	A	179–180	$C_{32}H_{29}N_7O_2$
8e	Cl	60	B	188–192 dec	$C_{30}H_{33}N_7O_2 \cdot 1.5H_2O$
8f	Cl	83	C	187–188	$C_{32}H_{35}N_7O_3 \cdot 0.2H_2O$
8g	Cl	67	B	212–214	$C_{33}H_{37}N_7O_2 \cdot 0.2H_2O$
8h	Cl	25	D	145–147	$C_{29}H_{29}N_6O_3 \cdot 0.5$acetone
9a	I	74	amorphous	102–105	$C_{32}H_{34}N_6O_4 \cdot 0.5H_2O$
9b	I	75	amorphous	92–95	$C_{31}H_{32}N_6O_5 \cdot 0.5H_2O$
9c	I	74	amorphous	102–105	$C_{33}H_{33}N_6O_5 \cdot 0.5CHCl_3$
9d	Br	71	E	123–125	$C_{31}H_{28}N_6O_5 \cdot 0.5H_2O$
10a	Cl	38	F	152–154 dec	$C_{27}H_{24}N_6O_5$
10b	Cl	60	F	145–150	$C_{28}H_{26}N_6O_5 \cdot 0.2$toluene
10c	Cl	36	G	96–100	$C_{29}H_{29}N_6O_5 \cdot 0.4$toluene
10d	Cl	53	F	143–145	$C_{29}H_{28}N_6O_5 \cdot 0.1$toluene
10e	I	69	A	144–147	$C_{30}H_{30}N_6O_5$
10f	Cl	54	A	136–138	$C_{31}H_{30}N_6O_5$
10g	Cl	54	A	140–142	$C_{32}H_{32}N_6O_5$
10h	Cl	46	A	138–142	$C_{32}H_{26}N_6O_5 \cdot 0.1$EtOAc$\cdot 0.5H_2O$
10i	Cl	55	A	146–147	$C_{34}H_{28}N_6O_5 \cdot 0.4$EtOAc
10j	Cl	31	H	105–107 dec	$C_{29}H_{26}N_6O_5 \cdot 0.5H_2O$
10k	Cl	67	I	142–144 dec	$C_{29}H_{28}N_6O_6 \cdot 0.5H_2O$
10l	I	69	I	147–148 dec	$C_{30}H_{28}N_6O_6 \cdot 0.1H_2O$
10m	I	63	I	142–144 dec	$C_{31}H_{30}N_6O_6$
10n	I	64	I	176–177 dec	$C_{32}H_{32}N_6O_6$
10o	I	44	amorphous	85–87	$C_{28}H_{28}N_6O_6 \cdot 0.3H_2O$
10p	Cl	33	amorphous	74–76	$C_{30}H_{30}N_6O_6 \cdot 1.5H_2O$
10q	I	45	amorphous	86–88 dec	$C_{32}H_{34}N_6O_6 \cdot 0.3H_2O$
10r	I	36	amorphous	95–97 dec	$C_{31}H_{30}N_6O_6 \cdot 0.5H_2O$
10s	I	65	I	163 dec	$C_{33}H_{34}N_6O_6$
10t	Cl	55	I	122–125 dec	$C_{28}H_{24}N_6O_6 \cdot CHCl_3$

[a] X indicates halides in R^1X used for alkylation of 3 and 4. [b] A = EtOAc–hexane; B = $CHCl_3$–MeOH; C = EtOAc–$CHCl_3$; D = acetone; E = benzene–CH_2Cl_2; F = toluene; G = toluene–hexane; H = acetone–ether–hexane; I = EtOH–H_2O. [c] All compounds gave satisfactory analyses C, H, N.

m), 7.93 (1H, dd, J = 1.2 and 8.0); IR (KBr) 1690 cm^{-1}. Anal. ($C_{45}H_{38}N_6O_2$) C, H, N.

Methyl 2-Butyl-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-carboxylate (8a). To an ice-cooled mixture of **6** (0.21 g, 0.30 mmol) and potassium carbonate (70 mg, 0.51 mmol) in DMF (2 mL) was added dropwise methyl iodide (68 mg, 0.48 mmol), and the resulting mixture was stirred at room temperature for 10 min. The reaction mixture was diluted with water and extracted with EtOAc. The extract was washed with water. After evaporation of the solvent, the residue was treated with 1 N HCl (0.4 mL) at room temperature for 1.5 h in MeOH (2 mL). The reaction mixture was concentrated in vacuo and extracted with $CHCl_3$. 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 ($CHCl_3$/MeOH = 20:1). The product was recrystallized from EtOAc–hexane to give **8a** (0.11 g, 79%) as colorless needles which was identified with authentic sample.[5a]

(±)-1-[[(Cyclohexyloxy)carbonyl]oxy]ethyl 2-Ethoxy-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-carboxylate (10s). A mixture of **7** (18.0 g, 26.4 mmol), cyclohexyl 1-chloroethyl carbonate (6.5 g, 31.5 mmol), potassium iodide (2.19 g, 13.2 mmol), and potassium carbonate (4.37 g, 31.6 mmol) in DMF (100 mL) was stirred at 60 °C for 2 h. The reaction mixture was diluted with water and extracted with EtOAc. The extract was washed with water. After evaporation of the solvent, the residue was treated with 1 N HCl (40 mL) at room temperature for 1.5 h in MeOH (150 mL)–$CHCl_3$ (30 mL). The reaction mixture was concentrated in vacuo 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 ($CHCl_3$/MeOH = 20:1). The product was recrystallized from EtOH–H_2O to give **10s** (10.5 g, 65.3%) as colorless crystals: mp 163 °C dec; ^1H NMR ($CDCl_3$) δ 1.13–1.84 (16H, m), 4.28–4.55 (3H, m), 5.65 (2H, d, J = 3.8), 6.72 (1H, q, J = 5.4), 6.81 (2H, d, J = 8.4), 6.93 (2H, d, J = 8.4), 7.03 (1H, t, J = 8.4), 7.22–7.23 (1H, m), 7.31–7.36 (1H, m), 7.52–7.60 (3H, m), 8.02–8.07 (1H, m); IR (KBr) 1750, 1720 cm^{-1}. Anal. ($C_{33}H_{34}N_6O_6$) C, H, N.

The compounds (**8d–g**, **9a–d**, **10a–r**, **10t**) were prepared by a procedure similar to that described above and the results were shown in Table IV.

Hydrolysis of Prodrugs to 3 or 4 in Vitro. Each prodrug was incubated in 1% small intestine homogenate, 2% liver homogenate, or 10% plasma prepared from rats at 37 °C. An aliquot sample was withdrawn at 10, 40, 60, 90 sec, 2, 5, 10, and 30 min after incubation and deproteinized with methanol. After centrifugation, the supernatant was evaporated in vacuo under centrifugation. The residue was dissolved in 1/15 M phosphate buffer, and injected into a high-performance liquid chromatograph (HPLC) to determine the concentration of **3** or **4** produced. The HPLC system consisted of a Shimadzu LC-9A pump, ODS column (150 × 4.6 mm i.d., Yamamura Chemical, Kyoto, Japan) and a Shimadzu SPD-6AV UV detector (258 nm). The mobile phase was 0.01 M KH_2PO_4/MeCN (55/45, v/v) with a flow rate of 1 mL/min.

Administration Studies. Male Sprague-Dawley rats (Clea Japan Inc., Tokyo, Japan), weighing about 300 g, were starved but allowed free access to water for 16–18 h before experiments.

Each parent drug was administered intravenously at a dose of 1 mg/kg. The blood was taken from opthalmic venus plexus at 0.0083, 0.00167, 0.25, 0.5, 1, 2, 3, 5, 7, and 24 h after injection and centrifuged to obtain plasma.

The parent drug (**3** or **4**) or each ester was given orally to rats at a dose of 10 mg/kg or 1 mg/kg as equivalent to **3** or **4**, respectively. The blood was taken to obtain plasma in a similar manner. The concentration of **3** or **4** in the plasma was determined by HPLC as described above.

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