Synthesis and Angiotensin II Receptor Antagonistic Activities of Benzimidazole Derivatives Bearing Acidic Heterocycles as Novel Tetrazole Bioisosteres[1]

Yasuhisa Kohara,* Keiji Kubo, Eiko Imamiya, Takeo Wada, Yoshiyuki Inada, and Takehiko Naka

Pharmaceutical Research Divisions, Pharmaceutical Group, Takeda Chemical Industries, Ltd., 17-85 Juso-honmachi 2-chome, Yodogawa-ku, Osaka 532, Japan

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The design, synthesis, and biological activity of benzimidazole-7-carboxylic acids bearing 5-oxo-1,2,4-oxadiazole, 5-oxo-1,2,4-thiadiazole, 5-thioxo-1,2,4-oxadiazole, and 2-oxo-1,2,3,5-oxathiadiazole rings are described. These compounds were efficiently prepared from the key intermediates, the amidoximes **4**. The synthesized compounds were evaluated for *in vitro* and *in vivo* angiotensin II (AII) receptor antagonistic activities. Most were found to have high affinity for the AT_1 receptor (IC_{50} value, 10^{-6}−10^{-7}M) and to inhibit the AII-induced pressor response (more than 50% inhibition at 1 mg/kg po). The 5-oxo-1,2,4-oxadiazole, 5-oxo-1,2,4-thiadiazole, and 5-thioxo-1,2,4-oxadiazole derivatives showed stronger inhibitory effects than the corresponding tetrazole derivatives, while their binding affinities were weaker. This might be ascribed to their improved bioavailability by increased lipophilicity. The 5-oxo-1,2,4-oxadiazole derivative **2** (TAK-536) and 5-oxo-1,2,4-thiadiazole derivative **8f** showed efficient oral bioavailability without prodrug formation. This study showed that the 5-oxo-1,2,4-oxadiazole ring and its thio analog, the 5-oxo-1,2,4-thiadiazole ring, could be lipophilic bioisosteres for the tetrazole ring in nonpeptide AII receptor antagonists.

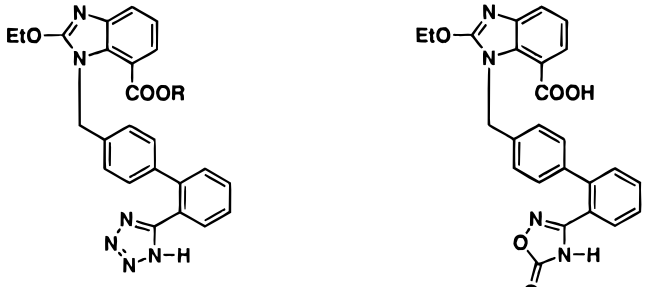
Introduction

The renin−angiotensin system (RAS) is known to play an important role in the regulation of blood pressure and electrolyte balance.[2] Inhibitors of the RAS would be effective for the treatment of hypertension and congestive heart failure. Although angiotensin-converting enzyme (ACE) inhibitors are highly effective and their use has become well-established for the treatment of hypertension and congestive heart failure, they suffer from some side effects such as dry cough and angioedema caused by the nonspecific action of ACE.[3] On the other hand, angiotensin II (AII) (the primary effector component of the RAS) receptor antagonists block the RAS at the AII receptor level and are expected to be more specific and effective agents than ACE inhibitors.

We have already reported the synthesis of benzimidazole-7-carboxylic acid derivatives such as **1a** (CV-11974, candesartan)[4] (Chart 1), novel and potent nonpeptide AT_1 selective AII receptor antagonists. The prodrug of **1a**, **1b** (TCV-116, candesartan cilexetil)[5] (Chart 1), is an orally active, highly effective, and long-acting AII receptor antagonist, and it is now under clinical trial as an antihypertensive agent. We have also demonstrated that two acidic moieties are very important for its highly potent AII receptor antagonistic activities.[6] Our research efforts have been focused on modification of the heterocyclic moieties (part A)[4−7] which are regarded as "templates" arranging three essential components: a lipophilic substituent, a tetrazolylbiphenylmethyl group, and a carboxyl group (Chart 2). As a result, the benzimidazole ring was found to be one of the most suitable templates.

We turned our attention to search for replacements of the biphenyl tetrazole moiety, especially the tetrazole ring (part B), because tetrazole derivatives have some

Chart 1. Structures of CV-11974 (**1a**), TCV-116 (**1b**), and TAK-536 (**2**)



1a : R = H
(CV-11974; candesartan)

2 (TAK-536)

1b : R = -CH(Me)OCOO-⬡
(TCV-116; candesartan cilexetil)

synthetic, metabolic, and chemical disadvantages. The synthesis of tetrazole derivatives could be dangerous due to the use of toxic and explosive azide compounds such as sodium azide or trialkyltin azide. Recently, losartan has been reported to be metabolized by N-glucuronidation on the tetrazole ring, which could shorten its *in vivo* duration.[8] Furthermore, some AII receptor antagonists possessing two acidic groups, a tetrazole ring and a carboxyl group, show low oral bioavailability because of their highly polar character. In some cases, prodrug approaches have been used to improve oral bioavailability.[5,9] Replacement of the tetrazole ring by other more lipophilic acidic groups has also been used to improve oral bioavailability, which would also solve the synthetic and metabolic problems. While many acylsulfonamide moieties have been introduced as bioisosteres of the tetrazole ring in AII receptor antagonists,[10] few heterocyclic moieties have been reported.[11] Thus, we started our investigation of replacement of the tetrazole ring by other heterocyclic rings

* Corresponding author: tel, +81-6-300-6120; fax, +81-6-300-6306; e-mail, Kohara_Yasuhisa@takeda.co.jp.

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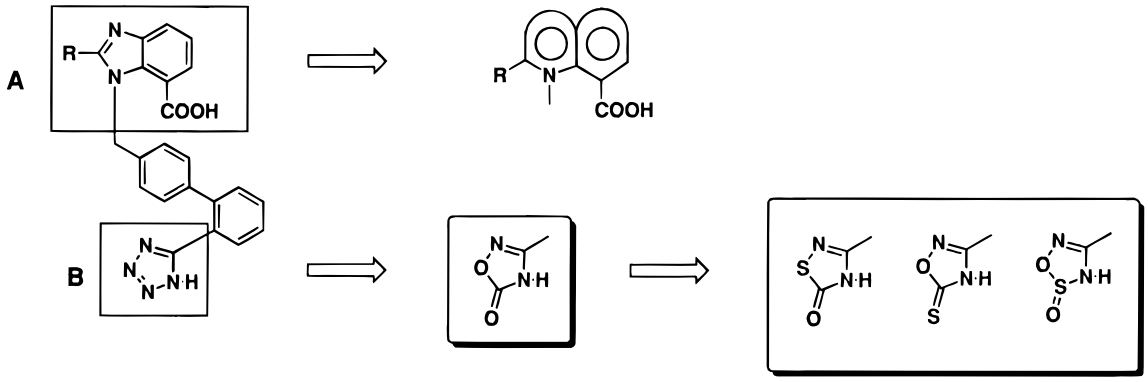
Chart 2. Our AII Receptor Antagonists



such as a thiazolidinedione ring, reported as a carboxylic acid bioisostere,[12] to find the 5-oxo-1,2,4-oxadiazole ring (Chart 2).[13] In our previous communication,[13] we described the synthesis and biological activities of a series of 2-substituted benzimidazole-7-carboxylic acids bearing the 5-oxo-1,2,4-oxadiazole ring which exhibited AII receptor antagonistic activities comparable to those of the tetrazole derivatives. The representative compound 1-[[2′-(2,5-dihydro-5-oxo-4*H*-1,2,4-oxadiazol-3-yl)-biphenyl-4-yl]methyl]-2-ethoxy-1*H*-benzimidazole-7-carboxylic acid, **2** (TAK-536) (Chart 1), was as potent and orally active as **1b** (TCV-116). Further studies have been conducted on the benzimidazole-7-carboxylic acids with the thio analogs of the 5-oxo-1,2,4-oxadiazole ring such as 5-oxo-1,2,4-thiadiazole ring, 5-thioxo-1,2,4-oxadiazole ring, and 2-oxo-1,2,3,5-oxathiadiazole ring. Here, we describe the preparation, AII receptor antagonistic activities, and structure−activity relationship (SAR) of 2-substituted benzimidazole-7-carboxylic acids possessing the thio analogs of the 5-oxo-1,2,4-oxadiazole ring as well as details of 5-oxo-1,2,4-oxadiazole derivatives.

Chemistry

The compounds prepared for this study are shown in Table 1, and the synthetic routes are outlined in Scheme 1. All compounds were synthesized from the common intermediates, amidoximes **4a**−**l**,[13] which were prepared by addition of hydroxylamine to the corresponding cyano derivatives **3a**−**l**.[4,7] The 5-oxo-1,2,4-oxadiazole series (**2**, **6**) was obtained from **4a**,**b** by treatment with 2-ethylhexyl chloroformate and cyclization in refluxing xylene followed by saponification. Compound **2** was prepared in kilogram scale without column chromatographic purification in this method.

The 5-oxo-1,2,4-thiadiazole series (**7a**−**l**) was synthesized by reaction of 1,1′-thiocarbonyldiimidazole (TCDI) with **4a**−**l** followed by treatment with silica gel or boron trifluoride diethyl etherate.[14] The obtained esters **7a**−**l** were hydrolyzed to afford the respective carboxylic acids **8a**−**l**.

The 5-thioxo-1,2,4-oxadiazole series (**10a**−**h**) was prepared from the amidoximes **4a**−**d**,**f**,**h**−**j** via two routes.[14] According to Birr's method,[15] **4a**−**d** were acetylated with acetic anhydride in the presence of triethylamine followed by treatment with carbon disulfide and sodium hydride to give the 5-thioxo-1,2,4-oxadiazoles **10a**−**d** in yields of 24−55%. Direct 5-thioxo-1,2,4-oxadiazole ring formation was accomplished in 50−59% yields (**10a**−**h**) by treatment of amidoximes **4f**,**h**−**j** with TCDI and base. The esters **10a**−**d**,**f**−**h** were hydrolyzed to give the corresponding carboxylic acids **11a**−**d**,**f**−**h**. In the case of the 2-ethoxy derivative **10e**, the carboxylic acid could not be isolated in pure state because it decomposed during purification.

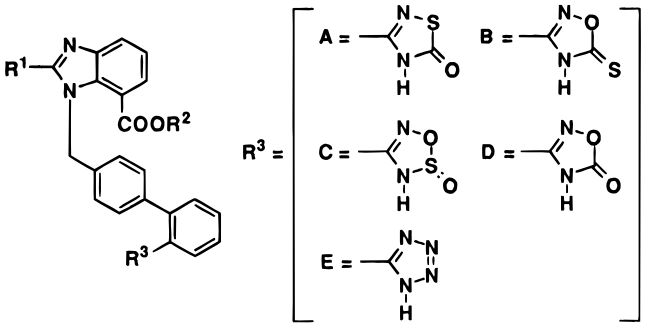
The 2-oxo-1,2,3,5-oxathiadiazole series (**12a**,**b**) was prepared in yields of 10% and 15%, respectively, by condensation of **4d**,**f** with thionyl chloride in the presence of pyridine.[16] The corresponding carboxylic acids could not be obtained in pure state because of their instability.

Pharmacological Results and Discussion

The compounds reported in this paper were evaluated for their binding affinity to the AII receptor with respect to inhibition of [^{125}I]AII (0.2 nM) binding to bovine adrenal cortical membranes as described previously.[7] The results are expressed as IC_{50} values and are listed in Table 1 alongside some tetrazole derivatives as references. Most carboxylic acids were found to have IC_{50} values of the order of 10^{-7} M.[17] With regard to the heterocyclic ring (R^3), the 5-oxo-1,2,4-thiadiazole (A), 5-thioxo-1,2,4-oxadiazole (B), and 5-oxo-1,2,4-oxadiazole (D) derivatives were found to be as potent as the tetrazole (E) derivatives (**8d**, **11d**, **6** vs **15**; **8f**, **2** vs **1a**). The effects of varying the side chain (R^1) at the 2-position of the benzimidazole ring on binding affinity were also examined. The optimal length of R^1 seemed to be two or three atoms (C, N, O, S) regardless of the nature of R^1 and the heterocyclic rings (R^3) (**8a**−**l**, **11a**−**d**,**f**−**h**). The binding affinities of the esters were generally inferior to those of the corresponding carboxylic acids (**7d** vs **8d**; **7f** vs **8f**; **10d** vs **11d**). These SAR were similar to those of the 5-oxo-1,2,4-oxadiazole[13] and the tetrazole derivatives previously reported.[4,7]

Each compound was further evaluated *in vivo* for inhibition of the pressor response induced by AII (100 ng/kg iv) in conscious rats,[7] and the data are listed in Table 1. With respect to the heterocyclic ring, the 5-oxo-1,2,4-thiadiazole (A) derivatives and 5-thioxo-1,2,4-oxadiazole (B) derivatives showed higher inhibitory potencies than the tetrazole (E) derivatives (**8d**, **11d** vs **15**; **8f** vs **1a**). The weaker *in vivo* activity of 2-oxo-1,2,3,5-oxathiadiazole (C) derivatives **12a**,**b** might be attributable to its instability in the body. Varying R^1 had effects similar to those on binding affinity, and the compounds with the chain length (R^1) of two or three atoms (C, N, O, S) displayed stronger potencies than those with longer or shorter chains. 2-Alkylamino derivatives **8k**,**l** clearly had less potent *in vivo* activity than the others despite high binding affinity. The dose

Table 1. Inhibitory Effects on the Specific Binding of [^{125}I]AII- and AII-Induced Pressor Responses in Rats



compd	R^1	R^2	R^3	receptor affinity IC_{50},10^{-7} M[a]	% inhibition[b] 3h/7h
7d	Bu	Me	A	>10	87/100 (10/35)[c]
7f	EtO	Me	A	7.5	100/100
8a	Me	H	A	9.7	80/71
8b	Et	H	A	0.69	100/100
8c	Pr	H	A	3.6	100/100
8d	Bu	H	A	7.2	92/83 (19/52)[c]
8e	MeO	H	A	3.6	88/91
8f	EtO	H	A	2.5	100/100 (100/100)[c]
8g	PrO	H	A	9.2	83/100
8h	MeS	H	A	5.0	100/100
8i	EtS	H	A	4.7	100/100
8j	PrS	H	A	>10	100/100
8k	MeNH	H	A	5.4	32/29
8l	EtNH	H	A	1.3	70/71
10d	Bu	Me	B	>10	84/87 (7/20)[c]
10e	EtO	Me	B	>10	83/93
11a	Me	H	B	>10	57/50
11b	Et	H	B	3.4	91/89
11c	Pr	H	B	3.9	96/94
11d	Bu	H	B	7.6	82/100 (19/57)[c]
11f	MeS	H	B	10	100/91
11g	EtS	H	B	6.9	100/100
11h	PrS	H	B	>10	100/100
12a	Bu	Me	C	>10	63/22[d]
12b	EtO	Me	C	4.6	35/29[d]
5a[f]	Bu	Me	D	9.0	NT[e]
5b[f]	EtO	Me	D	4.4	100/100[d]
6[f]	Bu	H	D	6.2	68/64
2[f] **(**TAK-536**)**	EtO	H	D	4.2	100/100 (75/64)[c]
13[g]	Bu	Me	E	3.2	47/27
14[h]	EtO	Me	E	0.66	100/90
15[g]	Bu	H	E	5.5	49/53
1a[h] (CV-11974)	EtO	H	E	1.1	100/92 (67/91)[c]
losartan				1.5	21/34

[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%. [b] Percent inhibition of AII (0.1 μg/kg iv)-induced pressor response at 3 and 7 h after administration of the test compounds (1 mg/kg po) in conscious male Sprague−Dawley rats. [c] Inhibition at a dose of 0.1 mg/kg po. [d] Inhibition at a dose of 3 mg/kg po. [e] NT means not tested. [f] **2**, **5a**,**b**, and **6** are reported in ref 13. [g] **13** and **15** are reported in ref 7. [h] **1a** and **14** are reported in ref 4.

dependency of the inhibitory effect on the pressor response of the representative compound 5-oxo-1,2,4-thiadiazole (A) derivative **8f** was studied, and the results are shown in Figure 1. At 0.01−1 mg/kg po, **8f** produced dose-dependent inhibition, which lasted for up to 24 h, and its ID_{50} value was (ID_{50} = 0.04 mg/kg) comparable to that of **2** (ID_{50} = 0.06 mg/kg).[13]

Lipophilicity, hydrophilicity, hydrogen bonding, and pK_a are likely to be important for the absorption, transport, and excretion of compounds.[18] In this study, modifications were designed to increase the lipophilicity of the tetrazole moiety in **1a**, which might cause disturbance of pK_a. The partition coefficient (log *P*) between 1-octanol and water,[13] pK_a[19] and oral bioavailability[5] were measured for the representative compounds (**1a**, **2**, **8f**), and the results are shown in Table 2. Increasing pK_a or percentage of neutral form leads to higher lipophilicity (log *P*). It is worth noting that compounds with higher lipophilicity (log *P*) show better oral bioavailability. **2** and **8f** were found to be absorbed efficiently upon oral administration without prodrug formation (BA = 20% and 51%, respectively). The acidity required for AII receptor antagonism seems to have a large range (pK_a = 5.3−6.6); however **2** and **8f** (IC_{50} = 4.2 × 10^{-7} and 2.5 × 10^{-7} M, respectively) showed slightly lower binding affinity than **1a** (IC_{50} = 1.1 × 10^{-7} M). Their improved BA could compensate for the loss of binding affinity to enhance *in vivo* activity. Replacement of the oxygen atom in the 5-oxo-1,2,4-oxadiazole ring with a sulfur atom, which is softer than the oxygen atom, caused not only higher lipophilicity and bioavailability but also faintly shorter duration (**8f** vs **2**) which might have been due to the susceptibility of the sulfur atom to metabolism. 1-[[2′-(2,5-Dihydro-5-oxo-4*H*-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl]-2-ethoxy-1*H*-benzimidazole-7-carboxylic acid (**2**, TAK-536) was selected and is currently undergoing clinical trials.

Conclusion

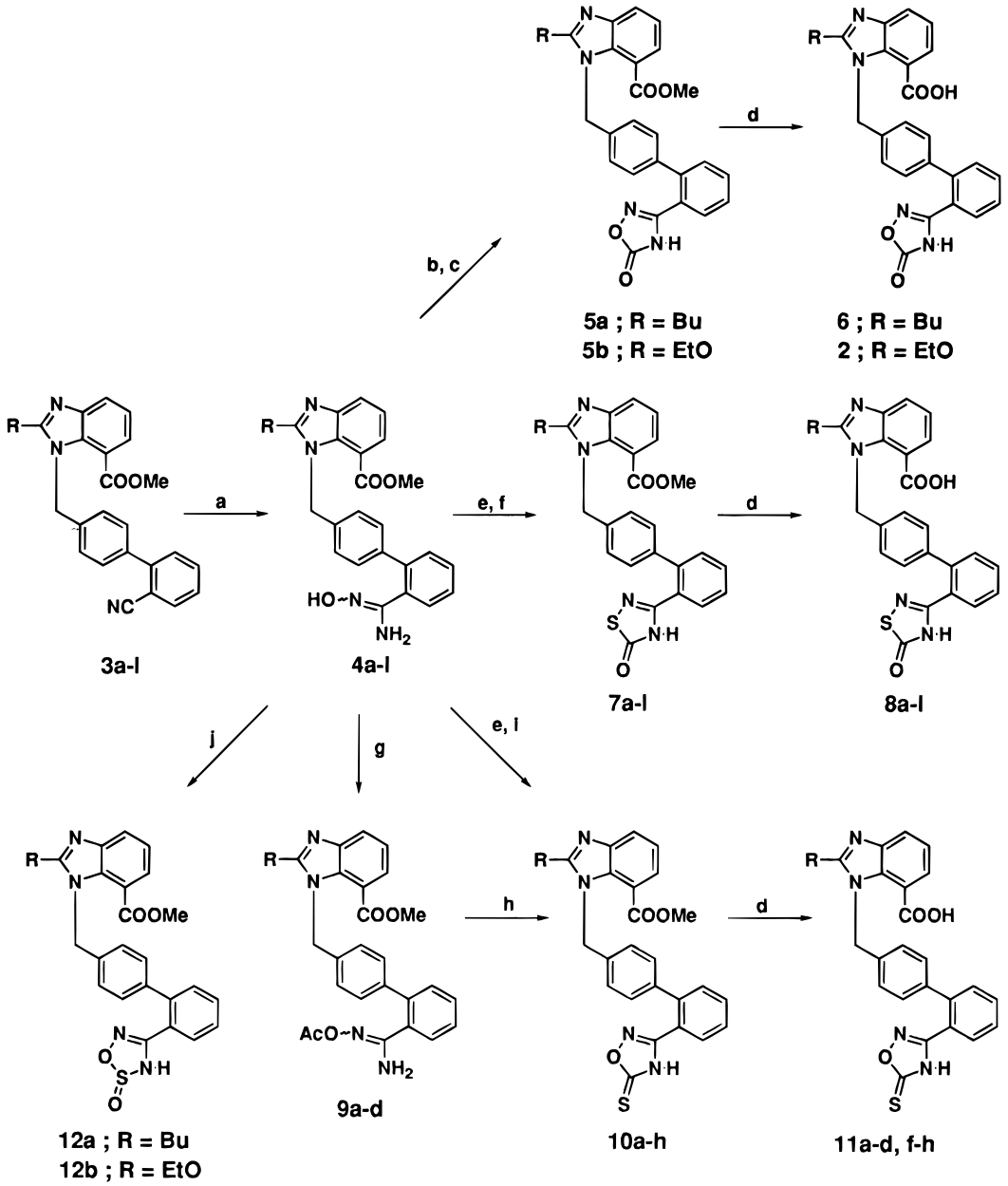
In this study, it was demonstrated that the oral bioavailability of **1a** could be improved by increasing its lipophilicity. The 5-oxo-1,2,4-oxadiazole ring and its thio analogs were found to be lipophilic bioisosteric replacements for the tetrazole ring in the potent AII receptor antagonist **1a**. The 5-oxo-1,2,4-oxadiazole (**2**, TAK-536) and 5-oxo-1,2,4-thiadiazole (**8f**) derivatives showed efficient oral BA and enhanced *in vivo* activity without prodrug formation comparable to **1b** (TCV-116). We believe that these acidic bioisosteres can be applied to modification of other acidic drugs.

Experimental Section

All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. The infrared (IR) spectra were recorded on a Hitachi 215 or a HORIBA FT-200 grating infrared spectrophotometer. The proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on 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, Merck Art. 7734 or Merck Art. 9385). The biological assays were performed as previously described.[7]

Methyl 2-Ethoxy-1-[[2′-(hydroxyamidino)biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-carboxylate (4f). Triethylamine (6.18 g, 61.1 mmol) was added to a suspension of hydroxylamine hydrochloride (4.24 g, 61.0 mmol) in DMSO (20 mL). An insoluble material was filtered off and washed with THF. The filtrate was concentrated *in vacuo* to remove THF, and methyl 1-[(2′-cyanobiphenyl-4-yl)methyl]-2-ethoxy-1*H*-benzimidazole-7-carboxylate (**3f**)[4] (5.00 g, 12.2 mmol) was added to the DMSO solution of hydroxylamine. After stirring at 75 °C for 15 h, the reaction mixture was diluted with water and extracted with EtOAc. The organic solution was extracted with 1 N HCl (25 mL). The aqueous solution was adjusted to pH 10 with 1 N NaOH and extracted with EtOAc. The organic solution was washed with water and dried (Na_2SO_4). The solvent was evaporated *in vacuo*, and the product was recrystallized from EtOAc−MeOH−hexane to give **4f** (2.97 g, 55%) as colorless needles: mp 207−209 °C; ^{1}H NMR ($CDCl_3$) δ 1.49 (3H, t, J = 7.1), 3.76 (3H, s), 4.35 (2H, brs), 4.68 (2H, q, J =

Scheme 1[a]



[a] (a)NH_2OH·HCl, Et_3N; (b) pyridine, 2-ethylhexyl chloroformate; (c) xylene, reflux; (d) aq NaOH or aq LiOH; (e) TCDI; (f) silica gel or BF_3·OEt_2; (g) Ac_2O, Et_3N; (h) NaH, CS_2; (i) DBU or DBN; (j) pyridine, $SOCl_2$.

7.1), 5.63 (2H, s), 6.99 (2H, d, J = 8.4), 7.16 (1H, t, J = 7.9), 7.28−7.56 (7H, m), 7.73 (1H, dd, J = 1.1, 7.9); IR (KBr) 3440, 3345, 1715, 1640, 1545, 1435, 1275, 1040, 760 cm^{-1}. Anal. ($C_{25}H_{24}N_4O_4$) C, H, N.

Compounds **4c**,**e**−**l** were prepared by a procedure similar to that described above, and the results are shown in Table 3. **4a**,**b**,**d**,**l** contaminated by amides were used for the next reaction without further purification.

Methyl 1-[[2′-(2,5-Dihydro-5-oxo-4*H*-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl]-2-ethoxy-1*H*-benzimidazole-7-carboxylate (5b). 2-Ethylhexyl chloroformate (25.3 g, 0.13 mol) was added dropwise to an ice-cooling mixture of **4f** (58.5 g, 0.13 mol) and pyridine (11.1 g, 0.14 mol) in DMF (220 mL). The resulting mixture was stirred at 0 °C for 30 min, 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 dissolved in xylene (800 mL). The solution was heated under reflux for 2 h. The reaction mixture was concentrated *in vacuo*, diluted with $CHCl_3$−EtOAc (3:1) (200 mL), and allowed to stand at room temperature. The precipitate was collected by filtration and washed with MeOH to give **5b** (32.2 g, 52%) as colorless prisms: mp 196−197 °C; ^{1}H NMR (DMSO-d_6) δ 1.40 (3H, t, J = 6.9), 3.68 (3H, s), 4.61 (2H, q, J = 7.0), 5.54 (2H, s), 7.00 (2H, d, J = 8.4), 7.15−7.26 (3H, m), 7.45−7.71 (6H, m); IR (Nujol) 1780, 1730, 1720, 1550, 1470, 1285, 1040, 760 cm^{-1}. Anal. ($C_{26}H_{22}N_4O_5$) C, H, N.

Methyl 2-Butyl-1-[[2′-(2,5-dihydro-5-oxo-4*H*-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-carboxylate (5a). This compound was prepared from **4d** by a procedure similar to that described above in 48% yield as colorless prisms: mp 232−233 °C; ^{1}H NMR ($CDCl_3$) δ 0.87 (3H, t, J = 7.2), 1.10−1.77 (4H, m), 2.47 (2H, t, J = 7.8), 3.63 (3H, s), 5.57 (2H, s), 6.57 (2H, d, J = 8.1), 6.73−7.93 (9H, m); IR (Nujol) 1770, 1720, 1260 cm^{-1}. Anal. ($C_{28}H_{26}N_4O_4$) C, H, N.

1-[[2′-(2,5-Dihydro-5-oxo-4*H*-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl]-2-ethoxy-1*H*-benzimidazole-7-carboxylic Acid (2, TAK-536). A mixture of **5b** (32.0 g, 68.0 mmol) and 0.4 N NaOH (500 mL, 0.20 mol) was stirred at 70 °C for 1.5 h. The reaction mixture was adjusted to pH 3 with 2 N HCl. The precipitate was collected by filtration and washed with EtOH to give **2** (29.2 g, 94%) as colorless prisms: mp 212−214 °C; ^{1}H NMR (DMSO-d_6) δ 1.47 (3H, t, J = 7.0), 4.67 (2H, q, J = 7.0), 5.77 (2H, s), 7.07−7.70 (11H, m); IR

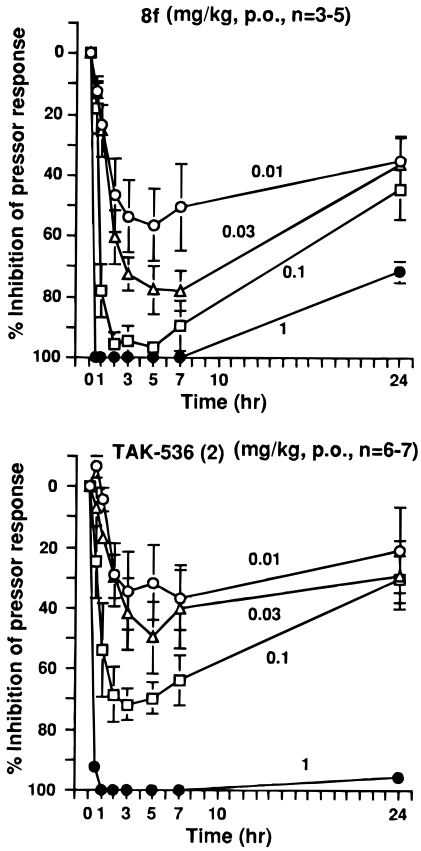
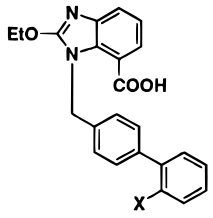
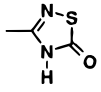
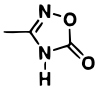


Figure 1. Inhibitory effects of **8f** and TAK-536 (**2**) on AII (100 ng/kg iv)-induced pressor response in conscious normotensive rats.

Table 2. pK_a, log *P*, and BA Values of the Acidic Heterocycles in AII Receptor Antagonists



compd	X	pK_a of X[a]	log P[b]	BA (%)[c]
8f		6.6	1.58	51
2 (TAK-536)		6.1	0.90	20
1a (CV-11974)		5.3	0.32	5.0

[a] A pK_a value was estimated using the corresponding methyl ester. All the pK_a's were determined in DMSO−H_2O (2:3) at 26 °C by potentiometric titration with standardized 0.1 N NaOH.[b] log *P* indicates the observed partition coefficient between 1-octanol and water.[13] [c] The bioavailability (BA) was determined as described previously.[5]

(Nujol) 1780, 1700, 1555, 1470, 1440, 1290, 1050, 765 cm^{-1}. Anal. ($C_{25}H_{20}N_4O_4$) C, H, N.

2-Butyl-1-[[2′-(2,5-dihydro-5-oxo-4*H*-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-carboxylic Acid (6). This compound was prepared from **8a** by a procedure similar to that described above in 64% yield as colorless prisms: mp 165−167 °C; ^{1}H NMR (DMSO-d_6) δ 0.90 (3H, t, J = 7.2), 1.13−2.00 (4H, m), 2.83 (2H, t, J = 7.0), 5.93 (2H, s), 6.93 (2H, d, J = 8.0), 7.13−7.90 (9H, m); IR (Nujol) 1770, 1700, 1440, 1420, 1250, 765 cm^{-1}. Anal. ($C_{27}H_{24}N_4O_4$·0.3$CHCl_3$) C, H, N.

Methyl 1-[[2′-(2,5-Dihydro-5-oxo-4*H*-1,2,4-thiadiazol-3-yl)biphenyl-4-yl]methyl]-2-ethyl-1*H*-benzimidazole-7-carboxylate (7b). A mixture of **4b** (0.40 g, 0.93 mmol) and TCDI (90%, 0.20 g, 1.01 mmol) in THF (5 mL) was stirred at room temperature for 1 h. After a suspension of silica gel (Merck Art. 9385) (4.0 g) in $CHCl_3$-MeOH (5:1) (50 mL) was added, the resulting mixture was stirred at room temperature for 23 h. Silica gel was filtered off and washed with $CHCl_3$−MeOH. The filtrate was concentrated *in vacuo*, and the residue was purified by flash column chromatography (EtOAc−hexane = 2:1 and then 3:1). The product was recrystallized from $CHCl_3$−Et_2O to give **7b** (0.11 g, 38%) as colorless crystals: mp 203−205 °C; ^{1}H NMR ($CDCl_3$) δ 1.13 (3H, t, J = 7.4), 2.62 (2H, q, J = 7.4), 3.53 (3H, s), 5.62 (2H, s), 6.60 (2H, d, J = 8.2), 6.87 (2H, d, J = 8.2), 6.80−7.90 (7H, m); IR (KBr) 1715, 1690, 1600, 1520 cm^{-1}. Anal. ($C_{26}H_{22}N_4O_3S$·0.5H_2O) C, H, N.

Compounds **7c**,**d**,**k**,**l** were prepared by a procedure similar to that described above, and the results are shown in Table 4.

Methyl 1-[[2′-(2,5-Dihydro-5-oxo-4*H*-1,2,4-thiadiazol-3-yl)biphenyl-4-yl]methyl]-2-ethoxy-1*H*-benzimidazole-7-carboxylate (7f). A mixture of **4f** (7.50 g, 16.9 mmol) and TCDI (90%, 4.01 g, 20.3 mmol) in THF (100 mL) was stirred at room temperature for 30 min. The 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 dissolved with THF (100 mL). After addition of boron trifluoride diethyl etherate (12.0 g, 84.5 mmol) to the solution, the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with water and extracted with EtOAc. The extract was washed with 1 N HCl 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 **7f** (2.90 g, 35%) as colorless needles: mp 209−211 °C; ^{1}H NMR ($CDCl_3$) δ 1.46 (3H, t, J = 6.9), 3.73 (3H, s), 4.57 (2H, q, J = 7.1), 5.67 (2H, s), 7.00−7.18 (5H, m), 7.28−7.33 (1H, m), 7.44−7.57 (4H, m), 7.82−7.86 (1H, m), 9.03 (1H, brs); IR (KBr) 1710, 1660, 1550, 1430, 1280, 1250, 1130, 1040, 745 cm^{-1}. Anal. ($C_{26}H_{22}N_4O_4S$) C, H, N.

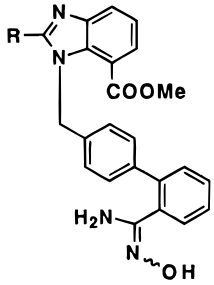
Compounds **7a**,**e**,**g**−**j** were prepared by a procedure similar to that described above, and the results are shown in Table 4.

Methyl 1-[[2′-(Acetoxyamidino)biphenyl-4-yl]methyl]-2-methyl-1*H*-benzimidazole-7-carboxylate (9a). A mixture of **4a** (2.00 g, 4.83 mmol), acetic anhydride (0.49 g, 4.80 mmol), and triethylamine (0.49 g, 4.84 mmol) in CH_2Cl_2 (20 mL) was stirred at room temperature for 2 h. The mixture 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 = 5:1, EtOAc, and then EtOAc−MeOH = 20:1) to give **9a** (1.26 g, 57%) as colorless crystals: mp 183−184 °C; ^{1}H NMR ($CDCl_3$) δ 2.14 (3H, s), 2.65 (3H, s), 3.76 (3H, s), 4.60 (2H, brs), 5.77 (2H, s), 6.91 (2H, d, J = 8.0), 7.20−7.70 (8H, m), 7.90 (1H, dd, J = 1.0, 8.0); IR (KBr) 1730, 1725, 1620, 1595, 1585, 1520 cm^{-1}. Anal. ($C_{26}H_{24}N_4O_4$·0.3H_2O) C, H, N.

Compounds **9b**−**d** were prepared by a procedure similar to that described above, and the results are shown in Table 6.

Methyl 1-[[2′-(2,5-Dihydro-5-thioxo-4*H*-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl]-2-methyl-1*H*-benzimidazole-7-carboxylate (10a). To an ice-cooling mixture of **9a** (0.60 g, 1.31 mmol) and carbon disulfide (0.38 g, 4.99 mmol) in DMF (8 mL) was added sodium hydride (60% in oil, 0.16 g, 4.00 mmol), and the resulting mixture was stirred at 0 °C for 50 min. The reaction mixture was diluted with 1 N HCl and extracted with EtOAc. The extract was washed with water and dried ($MgSO_4$). The solvent was evaporated *in vacuo*, and

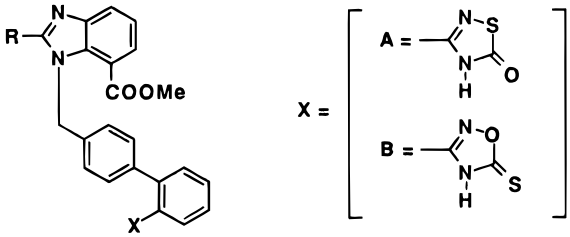
Table 3. Physicochemical Data of 1-[[2′-(Hydroxyamidino)biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-carboxylates



compd	R	yield, %	recryst solvent	mp, °C	formula[a]
4a	Me	68[b]			
4b	Et	61[b]			
4c	Pr	41	EtOAc−hexane	187−189	$C_{26}H_{26}N_4O_3 \cdot 0.3H_2O$
4d	Bu	61[b]			
4e	MeO	26	$CHCl_3$−EtOAc	203−204	$C_{24}H_{22}N_4O_4$
4f	EtO	55	EtOAc−MeOH−hexane	207−209	$C_{25}H_{24}N_4O_4$
4g	PrO	61	EtOAc	175−176	$C_{26}H_{26}N_4O_4$
4h	MeS	54	EtOAc−hexane	204−205	$C_{24}H_{22}N_4O_3S \cdot 0.5H_2O$
4i	EtS	58	EtOAc−hexane	137−139	$C_{25}H_{24}N_4O_3S \cdot 0.4H_2O$
4j	PrS	52	EtOAc−hexane	158−160	$C_{26}H_{26}N_4O_3S$
4k	MeNH	58	EtOAc−hexane	153−158	$C_{24}H_{23}N_5O_3 \cdot 0.5H_2O$
4l	EtNH	66[b]			

[a] **4c**,**e**−**k** gave satisfactory analyses (C, H, N). [b] Crude yields. These were used for the next reaction without purification.

Table 4. Physicochemical Data of 1-[[2′-(2,5-Dihydro-5-oxo-4*H*-1,2,4-thiadiazol-3-yl)biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-carboxylates and 1-[[2′-(2,5-Dihydro-5-thioxo-4*H*-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-carboxylates



compd	R	X	synthetic method[a]	yield, %	recryst solvent	mp, °C	formula[c]
7a	Me	A	B	8	$CHCl_3$−hexane	240−242 dec	$C_{25}H_{20}N_4O_3S$
7b	Et	A	A	38	$CHCl_3$−ether	203−205	$C_{26}H_{22}N_4O_3S \cdot 0.5H_2O$
7c	Pr	A	A	14	EtOAc−hexane	225−227 dec	$C_{27}H_{24}N_4O_3S \cdot 0.2H_2O$
7d	Bu	A	A	44	EtOAc−hexane	178−179	$C_{28}H_{26}N_4O_3S$
7e	MeO	A	B	45	$CHCl_3$−EtOAc	222−223	$C_{25}H_{20}N_4O_4S$
7f	EtO	A	B	35	EtOAc	211−212	$C_{26}H_{22}N_4O_4S$
7g	PrO	A	B	45	EtOAc	195−196	$C_{27}H_{24}N_4O_4S$
7h	MeS	A	B	45	EtOAc−MeOH	226−229 dec	$C_{25}H_{20}N_4O_3S_2 \cdot 0.5H_2O$
7i	EtS	A	B	42	$CHCl_3$−ether	232−233 dec	$C_{26}H_{22}N_4O_3S_2 \cdot 0.1H_2O$
7j	PrS	A	B	51	$CHCl_3$−ether	229−230 dec	$C_{27}H_{24}N_4O_3S_2$
7k	MeNH	A	A	11	$CHCl_3$	147−149	$C_{25}H_{21}N_5O_3S \cdot 0.3CHCl_3$
7l	EtNH	A	A	12	amorphous	127−133	$C_{26}H_{23}N_5O_3S \cdot 0.4CH_2Cl_2$
10a	Me	B	C	55	EtOAc−hexane	192−194	$C_{25}H_{20}N_4O_3S \cdot 0.5H_2O$
10b	Et	B	C	24	$CHCl_3$−ether	187−188	$C_{26}H_{22}N_4O_3S \cdot H_2O$
10c	Pr	B	C	29	EtOAc−hexane	206−209 dec	$C_{27}H_{24}N_4O_3S \cdot 0.2H_2O$
10d	Bu	B	C	32	EtOAc−hexane	180−181	$C_{28}H_{26}N_4O_3S$
10e	EtO	B	D	58	*b*	128−130 dec	$C_{26}H_{22}N_4O_4S \cdot EtOAc$
10f	MeS	B	E	50	EtOAc	185−187 dec	$C_{25}H_{20}N_4O_3S_2$
10g	EtS	B	E	59	EtOAc−hexane	160−162	$C_{26}H_{22}N_4O_3S_2$
10h	PrS	B	E	53	EtOAc−hexane	161−163	$C_{27}H_{24}N_4O_3S_2$

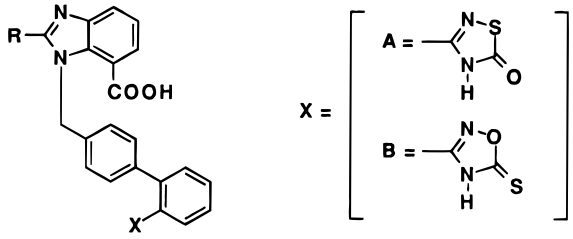
[a] Method A: (1) **4**, TCDI; (2) silica gel, $CHCl_3$−MeOH (5:1). Method B: (1) **4**, TCDI; (2) $BF_3 \cdot OEt_2$. Method C: **9**, CS_2, NaH, DMF. Method D: **4**, TCDI, DBN, CH_3CN. Method E: **4**, TCDI, DBU, CH_3CN. [b] **10e** was not recrystallized because it decomposed during the process. [c] All compounds gave satisfactory analyses (C, H, N).

the residue was purified by flash column chromatography ($CHCl_3$−MeOH = 50:1 and then 30:1) to give **10a** (0.33 g, 55%) as colorless crystals: mp 192−194 °C; ^{1}H NMR (DMSO-d_6) δ 2.59 (3H, s), 3.66 (3H, s), 5.72 (2H, s), 6.93 (2H, d, J = 8.0), 7.21 (2H, d, J = 8.0), 7.20−7.70 (6H, m), 7.85 (1H, dd, J = 1.2, 8.2); IR (KBr) 1720, 1600, 1520 cm^{-1}. Anal. ($C_{25}H_{20}N_4O_3S \cdot 0.5H_2O$) C, H, N.

Compounds **10b**−**d** were prepared by a procedure similar to that described above, and the results are shown in Table 4.

Methyl 1-[[2′-(2,5-Dihydro-5-thioxo-4*H*-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl]-2-ethoxy-1*H*-benzimidazole-7-carboxylate (10e). A mixture of **4f** (1.00 g, 2.25 mmol), TCDI (90%, 0.49 g, 2.47 mmol), and DBN (1.10 g, 8.86 mmol) in acetonitrile (20 mL) was stirred at room temperature for 4 h. The mixture was concentrated *in vacuo*, diluted with water, adjusted to pH 4−5 with 1 N HCl, and extracted with EtOAc. After the extract was concentrated *in vacuo*, the residue was dissolved with 1 N NaOH and washed with ether. The

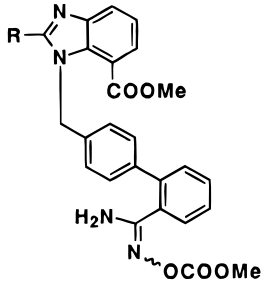
Table 5. Physicochemical Data of 1-[[2′-(2,5-Dihydro-5-oxo-4*H*-1,2,4-thiadiazol-3-yl)biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-carboxylic Acids and 1-[[2′-(2,5-Dihydro-5-thioxo-4*H*-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-carboxylic Acids



compd	R	X	synthetic method[a]	yield, %	recyrst solvent	mp, °C	formula[b]
8a	Me	A	F	60	EtOAc−MeOH	237−240 dec	$C_{24}H_{18}N_4O_3S·0.5EtOAc$
8b	Et	A	G	58	MeOH−$CHCl_3$−ether	204−207	$C_{25}H_{20}N_4O_3S·0.5CHCl_3$
8c	Pr	A	F	66	MeOH−EtOAc−hexane	228−230 dec	$C_{26}H_{22}N_4O_3S·0.2H_2O$
8d	Bu	A	G	82	EtOAc−MeOH	238−239 dec	$C_{27}H_{24}N_4O_3S·0.3H_2O$
8e	MeO	A	H	73	EtOAc−MeOH	203−205	$C_{24}H_{18}N_4O_4S$
8f	EtO	A	H	87	EtOAc−MeOH	213−214	$C_{25}H_{20}N_4O_4S$
8g	PrO	A	H	88	EtOAc−MeOH	204−206	$C_{26}H_{22}N_4O_4S$
8h	MeS	A	H	88	MeOH−EtOAc−ether	215−218 dec	$C_{24}H_{18}N_4O_3S_2$
8i	EtS	A	H	90	EtOAc−hexane	210−212 dec	$C_{25}H_{20}N_4O_3S_2$
8j	PrS	A	H	75	EtOAc−hexane	135−140	$C_{26}H_{22}N_4O_3S_2$
8k	MeNH	A	I	91	EtOH	320−321 dec	$C_{24}H_{19}N_5O_3S·0.6H_2O$
8l	EtNH	A	I	80	EtOAc−EtOH	281−283 dec	$C_{25}H_{21}N_5O_3S·0.3H_2O$
11a	Me	B	F	85	$CHCl_3$−MeOH	249−255 edc	$C_{24}H_{18}N_4O_3S$
11b	Et	B	J	90	$CHCl_3$−MeOH	240−245 dec	$C_{25}H_{20}N_4O_3S·0.5H_2O$
11c	Pr	B	H	76	$CHCl_3$−MeOH	187−191 dec	$C_{26}H_{22}N_4O_3S·0.9H_2O$
11d	Bu	B	J	42	EtOH	178−180	$C_{27}H_{24}N_4O_3S$
11f	MeS	B	H	68	EtOAc−hexane	186−190 dec	$C_{24}H_{18}N_4O_3S_2$
11g	EtS	B	H	64	EtOAc−hexane	163−165 dec	$C_{25}H_{20}N_4O_3S_2·0.8H_2O$
11h	PrS	B	H	81	EtOAc−hexane	147−150 dec	$C_{26}H_{22}N_4O_3S_2$

[a] Method F: **7** or **10**, LiOH·H_2O, MeOH−H_2O. Method G: **7**, 1 N NaOH, MeOH. Method H: **7** or **10**, LiOH·H_2O, THF-H_2O. Method I: **7**, 0.1 N NaOH, MeOH. Method J: **10**, 2N NaOH, MeOH. [b] All compounds gave satisfactory analyses (C, H, N).

Table 6. Physicochemical Data of 1-[[2′-(Acetoxyamidino)-biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-carboxylates



compd	R	yield, %	recryst solvent	mp, °C	formula[a]
9a	Me	57	EtOAc−hexane	183−184	$C_{26}H_{24}N_4O_4·0.3H_2O$
9b	Et	80	EtOAc−hexane	187−188	$C_{27}H_{26}N_4O_4$
9c	Pr	86	EtOAc−hexane	177−178	$C_{28}H_{28}N_4O_4·0.1H_2O$
9d	Bu	98	EtOAc−hexane	170−173	$C_{29}H_{30}N_4O_4$

[a] All compounds gave satisfactory analyses (C, H, N).

aqueous solution was adjusted to pH 4 with 1 N HCl, and extracted with EtOAc. The extract was washed with water and dried ($MgSO_4$). The solvent was evaporated *in vacuo*, and the residue was washed with EtOAc to give **10e** (0.57 g, 65%) as pale yellow crystals: mp 121−123 °C dec; ^{1}H NMR ($CDCl_3$) δ 1.42 (3H, t, J = 6.9), 3.66 (3H, s), 4.39 (2H, q, J = 7.0), 5.65 (2H, s), 6.90−7.11 (6H, m), 7.29−7.33 (1H, m), 7.50 (1H, dd, J = 1.4, 7.4), 7.53−7.61 (2H, m), 7.81−7.86 (1H, m); IR (KBr) 1720, 1545, 1480, 1470, 1435, 1280, 1250, 1040, 780 cm^{-1}. Anal. ($C_{26}H_{22}N_4O_4S$·EtOAc) C, H, N.

Methyl 1-[[2′-(2,5-Dihydro-5-thioxo-4*H*-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl]-2-(methylthio)-1*H*-benzimidazole-7-carboxylate (10f). A mixture of **4h** (0.57 g, 1.25 mmol), TCDI (90%, 0.37 g, 1.87 mmol), and DBU (0.76 g, 4.99 mmol) in acetonitrile (10 mL) was stirred at room temperature for 1 h. The mixture was diluted with water, adjusted to pH 4 with 1 N HCl, 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 purified by flash column chromatography (EtOAc−hexane = 5:1). The product was recrystallized from EtOAc to give **10f** (0.31 g, 50%) as colorless crystals: mp 185−187 °C dec; ^{1}H NMR ($CDCl_3$) δ 2.67 (3H, s), 3.78 (3H, s), 5.76 (2H, s), 7.03 (2H, d, J = 8.0), 7.15 (1H, t, J = 7.9), 7.17 (2H, d, J = 8.0), 7.38 (1H, dd, J = 1.3, 7.5), 7.49−7.68 (4H, m), 7.84 (1H, dd, J = 1.7, 7.5); IR (KBr) 1715, 1485, 1470, 1460, 1450, 1415, 1280, 1255, 1180, 1140, 755, 740 cm^{-1}. Anal. ($C_{25}H_{20}N_4O_3S_2$) C, H, N.

Compounds **10g**,**h** were prepared by a procedure similar to that for the preparation of **10f**, and the results are shown in Table 4.

Methyl 2-Ethoxy-1-[[2′-(2-oxo-3*H*-1,2,3,5-oxathiadiazol-4-yl)biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-carboxylate (12b). To an ice-cooling mixture of **4f** (2.00 g, 4.50 mmol) and pyridine (0.71 g, 8.98 mmol) in THF (100 mL) was added dropwise a solution of thionyl chloride (0.54 g, 4.54 mmol) in CH_2Cl_2 (20 mL), and the resulting mixture was stirred at the same temperature for 45 min. The reaction mixture was concentrated *in vacuo*, diluted with water, 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 ($CHCl_3$−EtOAc−MeOH = 60:10:1 and then 30:1:2). The product was recrystallized from EtOAc to give **12b** (0.35 g, 16%) as colorless prisms: mp 109−110.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.50 (3H, t, J = 7.0), 3.78 (3H, s), 4.62 (2H, q, J = 7.0), 5.60 (2H, s), 6.99 (2H, d, J = 8.2), 7.11−7.66 (8H, m), 7.90 (1H, dd, J = 1.3, 7.5); IR (KBr) 1720, 1550, 1430, 1280, 1040, 755 cm^{-1}. Anal. ($C_{25}H_{22}N_4O_5S·0.2H_2O$) C, H, N.

Methyl 2-Butyl-1-[[2′-(2-oxo-3*H*-1,2,3,5-oxathiadiazol-4-yl)biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-carboxylate (12a). This compound was prepared from **4d** by a procedure similar to that described above in 18% yield as colorless prisms: mp 124−125 °C; ^{1}H NMR ($CDCl_3$) δ 0.93 (3H, t, J = 7.2), 1.30−1.49 (2H, m), 1.62−1.79 (2H, m), 2.64 (2H, t, J = 7.8), 3.70 (3H, s), 5.64 (2H, s), 6.74 (2H, d, J = 8.1), 7.09−7.62 (8H, m), 7.89 (1H, dd, J = 1.7, 7.4); IR (KBr) 1720, 1520, 1450, 1435, 1410, 1285, 1185, 1120, 760 cm^{-1}. Anal. ($C_{27}H_{26}N_4O_4S·0.2iPr_2O·0.2H_2O$) C, H, N.

1-[[2′-(2,5-Dihydro-5-oxo-4*H*-1,2,4-thiadiazol-3-yl)biphenyl-4-yl]methyl]-2-ethoxy-1*H*-benzimidazole-7-carboxylic Acid (8f). A mixture of **10f** (2.40 g, 4.93 mmol) and $LiOH·H_2O$ (0.52 g, 12.4 mmol) in THF (25 mL)−H_2O (15 mL) was stirred at room temperature for 19 h. The reaction mixture was diluted with water and acidified with 1 N HCl. The precipitate was collected by filtration and recrystallized from $CHCl_3$−MeOH to give **8f** (2.04 g, 87%) as colorless needles: mp 213−214 °C; ^{1}H NMR (DMSO-d_6) δ 1.39 (3H, t, J = 7.0), 4.58 (2H, q, J = 7.0), 5.66 (2H, s), 7.02 (2H, d, J = 8.2), 7.14−7.22 (3H, m), 7.43−7.69 (6H, m); IR (KBr) 1700, 1660, 1550, 1280, 1240, 1040, 765, 750 cm^{-1}. Anal. ($C_{25}H_{20}N_4O_3S$) C, H, N.

The compounds **8a**−**e**,**g**−**l** and **11a**−**d**,**f**−**h** were prepared by a procedure similar to that described above, and the results are shown in Table 5.

Acknowledgment. We wish to thank Dr. K. Nishikawa for his encouragement and helpful discussion throughout this work and Ms. M. Ojima for her technical assistance.

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