Synthesis and Evaluation of Novel Nonpeptide Angiotensin II Receptor Antagonists: Imidazo[4,5-*c*]pyridine Derivatives with an Aromatic Substituent

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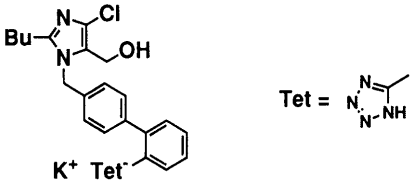
Received August 29, 1994; accepted November 15, 1994

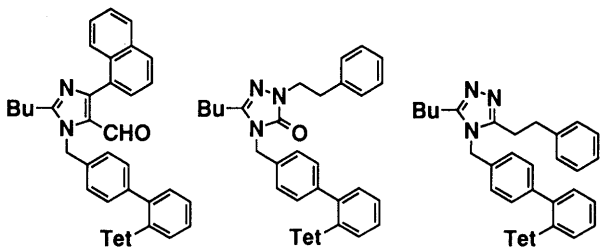
Starting from recently reported nonpeptidic angiotensin II (AII) receptor antagonists, we have designed and prepared a new series of 6-arylimidazo[4,5-*c*]pyridine derivatives. Variation of phenyl groups at the 4-, 6- or 7-position of imidazo[4,5-*c*]pyridine showed that substitution at the 6-position resulted in receptor-binding activity almost as potent as that of DuP 753. This led to synthesis and evaluation of an extensive series of 6-aryl-imidazo[4,5-*c*]pyridine derivatives. Some of them were 4-fold more potent *in vitro* than DuP 753, but only showed weak antihypertensive activity *in vivo* when given orally to rats.

Key words imidazo[4,5-*c*]pyridine; angiotensin II; receptor antagonist; antihypertensive agent; synthesis

The renin–angiotensin system plays a major role in the regulation of blood pressure and electrolyte homeostasis.[1] Angiotensin II (AII) has recently been noted to be not only a potent vasoconstrictor and a stimulator of aldosterone secretion, but also a cell growth factor stimulating neointima formation of vascular smooth muscles.[2] Although some peptidic AII receptor antagonists such as saralasin are known, their therapeutic utility is limited due to poor oral bioavailability, short plasma half-life and partial agonist activity. Recently, several nonpeptidic AII receptor antagonists which lack the defects of the peptidic antagonists have been reported.[3] The therapeutic profile of AII receptor antagonists is thought to be similar to that of angiotensin converting enzyme (ACE) inhibitors such as captopril, enalapril, and lisinopril. In addition, since AII receptor antagonists do not affect the metabolism of bradykinin, they may not have the side effects of ACE inhibitors, such as causing dry cough. The first orally active AII receptor antagonist DuP 753 (Losartan) reported by DuPont,[4] is entering late clinical development, and several more potent compounds have been disclosed.[5] Most of these compounds have a variety of heterocycles that incorporate an alkyl group and a biphenyltetrazole substituent, and some of them have an aromatic ring in the region near the heterocyclic ring[6] (Fig. 1).



DuP 753
(Losartan)



DuPont Searle Merck

Fig. 1

We presumed that a lipophilic pocket which accepts an aromatic ring of an antagonist molecule exists in the AII receptor and that the aromatic moiety plays an important role in receptor binding. In this article, several different aromatic substituents were introduced into the imidazo-[4,5-*c*]pyridine derivatives (**1l**, **2l**) reported by Merck,[5f] in order to evaluate the influence of the aromatic substituent. Imidazo[4,5-*b*]pyridine derivatives are well known as AII receptor antagonists,[5f] whereas imidazo-[4,5-*c*]pyridines have not been well studied. We report here a new series of AII receptor antagonists, *i.e.*, 2-alkylimidazo[4,5-*c*]pyridine derivatives substituted with an aromatic ring at the 4-, 6- or 7-position (Fig. 2).

Chemistry

The 2-alkyl-6-arylimidazo[4,5-*c*]pyridines **1** and **2** were prepared *via* 6-aryl-3-carboxy-4(1*H*)-pyridone key intermediates **5**. Previously, we found a new method for synthesis of 6-aryl-3-carboxy-4(1*H*)-pyridones (Chart 1).[7] Ethyl 2-acetyl-3-aminoacrylate (**3**)[8] derived from ethyl 3-oxobutyrate was deprotonated with 2.6 eq of sodium hydride, and then acylated with various aryl esters to generate the intermediates **4**, which were easily cyclized to the corresponding pyridone derivatives **5** (Table I).

During the course of this research, the Schering–Plough

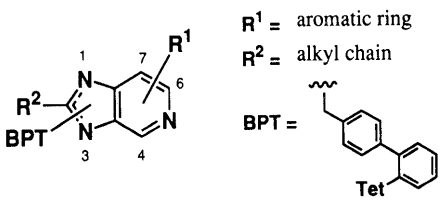


Fig. 2

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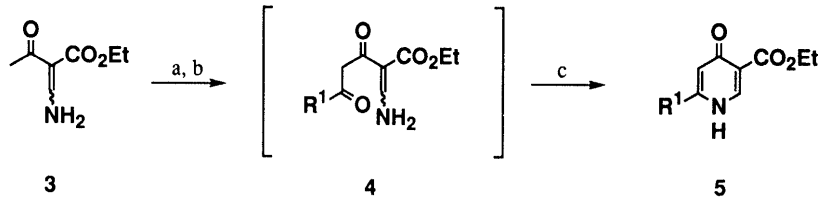
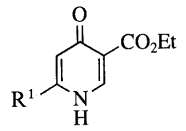


reagents: (a) NaH / THF; (b) R^1CO_2Et / THF; (c) Δ

Chart 1. Preparation of the Pyridone Intermediates **5**

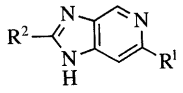
TABLE I. Physicochemical Data of the Pyridone Intermediates **5**



Compd.	R^1	% yield[a]	mp (°C)	Formula[b]
5a	Phenyl	43	120—121	$C_{14}H_{13}NO_3$
5b	2-Cl-Phenyl	51	139—141	$C_{14}H_{12}ClNO_3$
5c	3-CF_3-Phenyl	55	131—132	$C_{15}H_{12}F_3NO_3$
5d	Thiophen-2-yl	44	107—108	$C_{12}H_{11}NO_3S$
5e	Furan-2-yl	44	104—105	$C_{12}H_{11}NO_4$

a) See Experimental for representative procedures. *b*) Analytical results were within ±0.3% of the theoretical values.

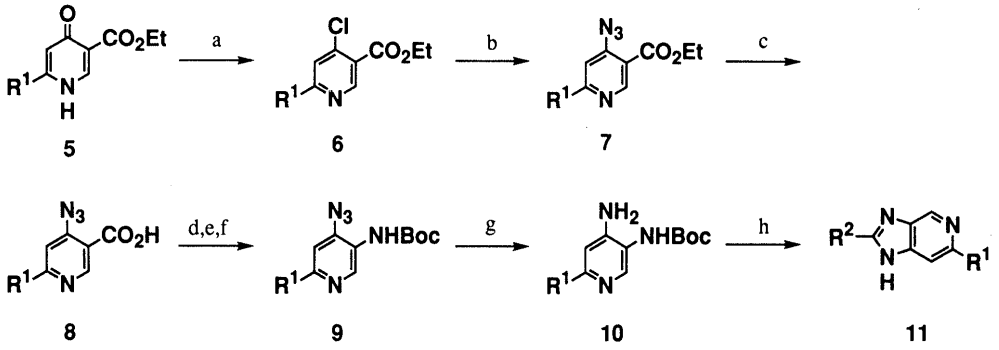
TABLE II. Physicochemical Data of the Imidazo[4,5-*c*]pyridine Intermediates **11**



11

Compd.	R^1	R^2	mp (°C)	Formula[a]
11a	Phenyl	*n*-Butyl	191—193	$C_{16}H_{17}N_3$
11b	Phenyl	Ethyl	213—215	$C_{14}H_{13}N_3$
11c	Phenyl	*n*-Propyl	209—211	$C_{15}H_{15}N_3$
11d	Phenyl	Cyclopropyl	238—240	$C_{15}H_{13}N_7$
11e	Phenyl	*n*-Pentyl	157—158	$C_{17}H_{19}N_3$
11f	2-Cl-Phenyl	*n*-Propyl	164—165	$C_{15}H_{14}ClN_3$
11g	2-Cl-Phenyl	*n*-Butyl	138—140	$C_{16}H_{16}ClN_3$
11h	3-CF_3-Phenyl	*n*-Propyl	156—157	$C_{16}H_{14}F_3N_3$
11i	Thiophen-2-yl	*n*-Propyl	186—188	$C_{13}H_{13}N_3S$
11j	Thiophen-2-yl	*n*-Butyl	174—176	$C_{14}H_{15}N_3S$
11k	Furan-2-yl	*n*-Propyl	212—214	$C_{13}H_{13}N_3O$

a) Analytical results were within ±0.3% of the theoretical values.



reagents: (a) $POCl_3$; (b) NaN_3 / DMF; (c) KOH / EtOH / H_2O; (d) $ClCO_2Et$ /Et_3N / THF; (e) NaN_3 / H_2O; (f) *tert*-BuOH / $ClCH_2CH_2Cl$; (g) $SnCl_2 \cdot 2H_2O$ / NaOH / EtOH / THF; (h) R^2-CO_2H / PPA

Chart 2. Preparation of the 6-Arylimidazo[4,5-*c*]pyridine Intermediates **11**

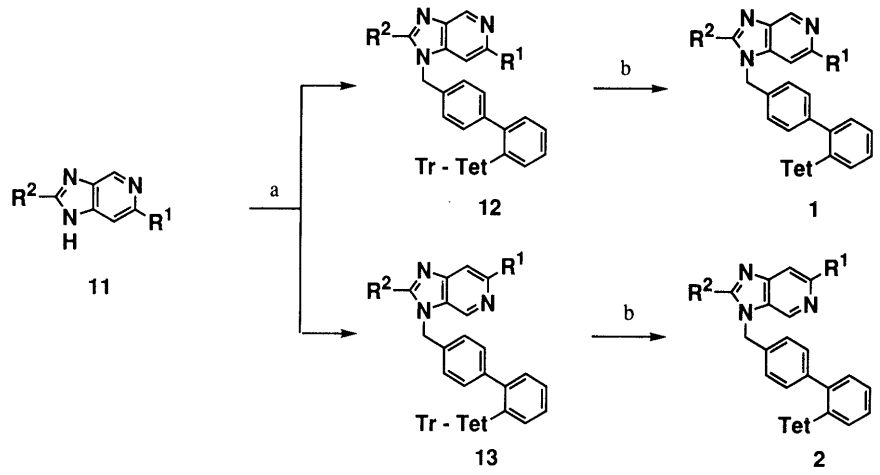
group[9] published an alternative method for the synthesis starting from ethyl 2-acetyl-3-dimethylaminoacrylate instead of **3**, using $LiN(SiMe_3)_2$ and ArCOCl. In their method, the dimethylamino group was eliminated to afford a γ-pyrone intermediate through nucleophilic attack by the enolate oxygen. Next, the oxygen atom was replaced with a nitrogen atom by treatment with NH_4OAc to give a pyridone product. In our method, the amino group of the intermediate serves as a nucleophile, and the cyclization to pyridone occurs directly. Both synthetic methods are superior to the conventional ones[10] in terms of yield and convenience.

The pyridone intermediates **5** were converted to the 6-arylimidazo[4,5-*c*]pyridine derivatives **11** by the route shown in Chart 2. The reaction of **5** in refluxing phosphorus oxychloride gave the chloropyridine **6**, which was then heated with sodium azide to give **7**. Alkaline hydrolysis of **7** afforded the carboxylic acids **8**. Mixed anhydride formation of **8** followed by treatment with aqueous sodium azide gave acylazide intermediates, which were then submitted to Curtius rearrangement in *tert*-BuOH, generating the protected amino derivatives **9**. The azide group of **9** was reduced with stannous chloride to give **10**. The following deprotection with concomitant cyclization was accomplished by heating **10** with appropriate acids in polyphosphoric acid to give 6-arylimidazo[4,5-*c*]pyridines **11** (Table II).

Alkylation of **11** with 5-(4′-bromomethylbiphenyl-2-yl)-

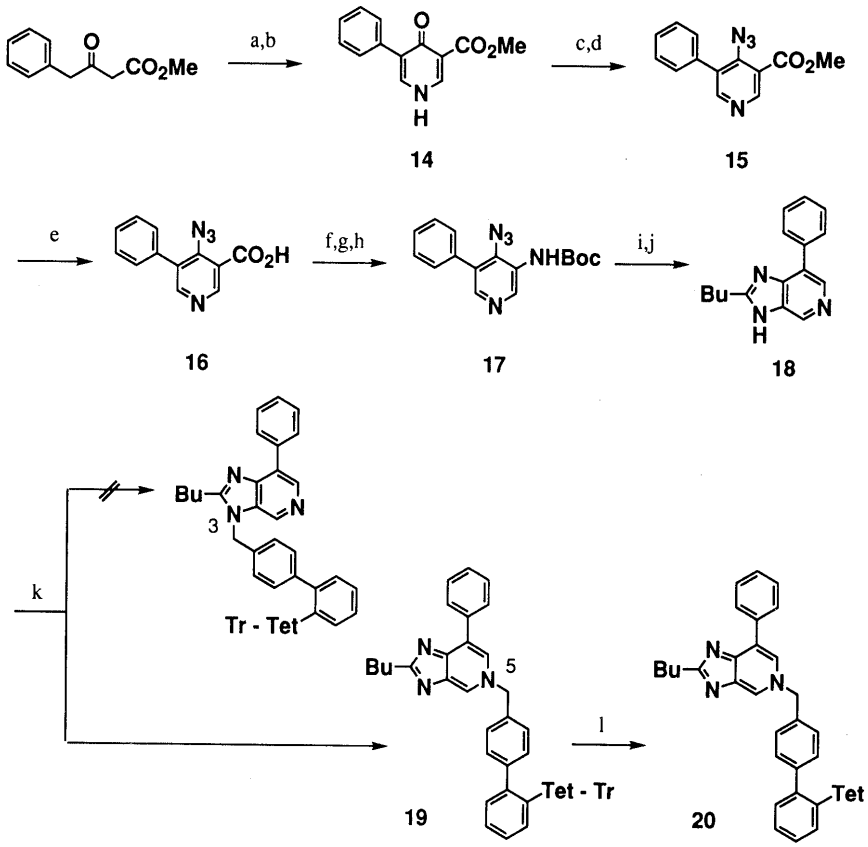
2-trityl-2*H*-tetrazole[4] in the presence of sodium hydride gave two positional isomers in the ratio of about 2:1 (Chart 3). The two isomeric products **12** and **13** were assigned unambiguously on the basis of nuclear Overhauser effect (NOE) difference spectroscopy of the final products **1** and **2**, which were derived by deprotection of the trityl group. In the ^{1}H-NMR spectrum of the major isomer, an NOE was observed between benzylic methylene protons and a proton at the 7-position of imidazopyridine. On the other hand, the NOE study of the minor one showed a correlation between benzylic methylene protons and a proton at the 4-position of imidazopyridine. These results supported the assignment of the major isomer as the 1*H*-derivative **1** and the minor one as the 3*H*-derivative **2**.

The preparation of the 7-phenylimidazo[4,5-*c*]pyridine



reagents: (a) 5-(4'-bromomethylbiphenyl-2-yl)-2-trityl-2*H*-tetrazole / NaH / DMF; (b) conc. HCl / MeOH

Chart 3. Preparation of the AII Antagonists **1** and **2**



reagents: (a) DMF-acetal / xylene; (b) NH_4OAc; (c) $POCl_3$; (d) NaN_3 / DMF; (e) KOH / EtOH / H_2O;(f) $ClCO_2Et$ / Et_3N / THF; (g) NaN_3 / H_2O; (h) *tert*-BuOH / $ClCH_2CH_2Cl$; (i) $SnCl_2 \cdot 2H_2O$ / NaOH / EtOH / THF; (j) *n*-Bu-CO_2H / PPA; (k) 5-(4'-bromomethylbiphenyl-2-yl)-2-trityl-2*H*-tetrazole / NaH / DMF; l) conc. HCl / MeOH

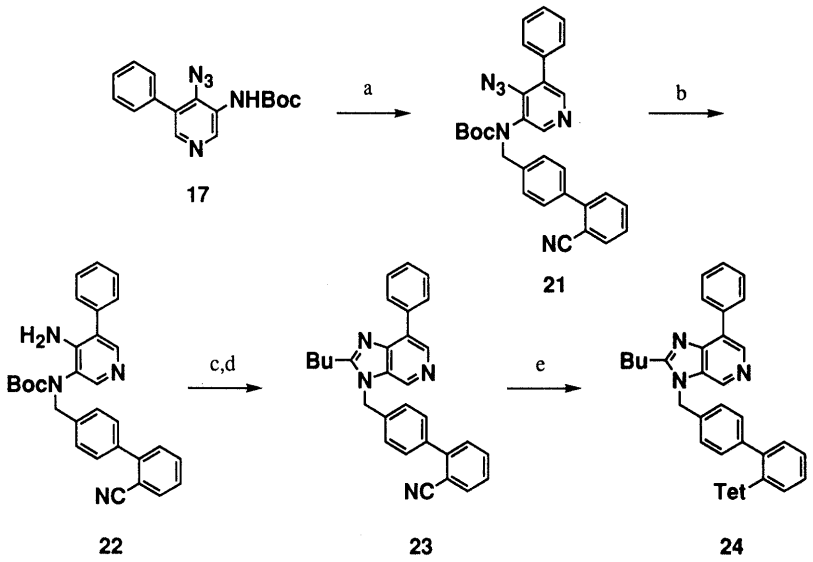
Chart 4

derivative **24** was tried according to the route shown in Chart 4. The pyridone **14** derived from methyl 3-oxo-4-phenylbutyrate was converted to **18** in a similar manner for preparation of the 6-aryl isomers **11**. However, alkylation of **18** did not proceed at the desired 3-position, but gave only the 5-substituted derivative **19**. The structure of **19** was confirmed by means of an NOE study after conversion of **19** into **20**. The NOE study of **20** showed the benzylic methylene protons to be correlated with protons at both the 4- and 6-positions of the imidazo-[4,5-*c*]pyridine ring.

Therefore, as shown in Chart 5, **17** was alkylated with 4′-bromomethylbiphenyl-2-carbonitrile[4)] prior to imidazole ring formation. The alkylation product **21** was reduced with stannous chloride to give **22**. Deprotection of **22** with TFA followed by cyclization with trimethyl orthovalerate gave the 3-substituted 7-phenylimidazo[4,5-*c*]pyridine derivative **23**. The nitrile **23** was converted to the target compound **24** by treatment with trimethyltinazide.

Finally, the 4-phenylimidazo[4,5-*c*]pyridine derivative **35** was prepared according to the route described below. Triethyl orthobenzoate and 3-oxobutyronitrile were condensed in the presence of acetic anhydride to give **25**. The ethoxy group of **25** was replaced with an amino group by treatment with NH_3–MeOH. Conversion of **26** to **28** was effectively performed by using 2 eq of Vilsmeier reagent. This reaction was postulated to involve the intermediate **27** (Chart 6). This hypothesis was confirmed by the fact that stepwise reaction of **26** with 1 eq of *N*,*N*-dimethylformamide (DMF)-acetal and then 1 eq of Vilsmeier reagent afforded the same product **28**. This reaction was found to be very useful for the preparation of 2-aryl-4-chloro-3-nicotinonitrile from various aryl orthoesters.

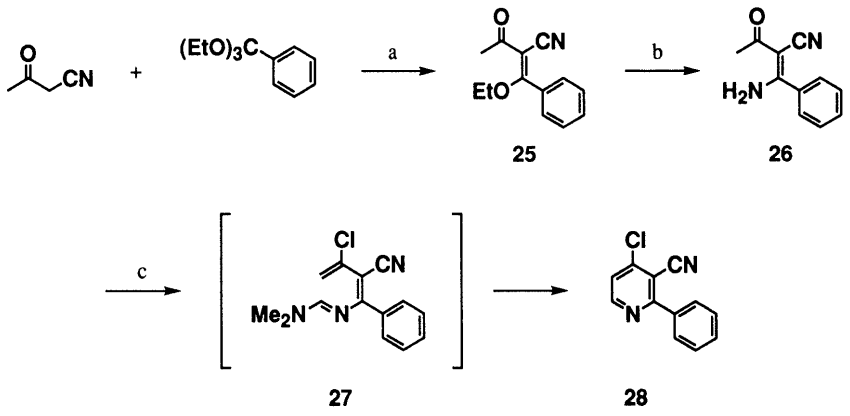
The chloropyridine **28** was converted to the azide **29**. After acidic hydrolysis of the nitrile group of **29**, the resulting **30** was converted to **31** by Hofmann rearrangement. Subsequently, **31** was transformed to the target compound **35** in a manner similar to that described for **1**.



17 21 22 23 24

reagents: (a) 4'-bromomethylbiphenyl-2-carbonitrile / NaH / DMF; (b) $SnCl_2 \cdot 2H_2O$ / NaOH / EtOH / THF; (c) TFA / CH_2Cl_2; (d) *n*-$BuC(OMe)_3$ / AcOH; (e) Me_3SnN_3 / xylene

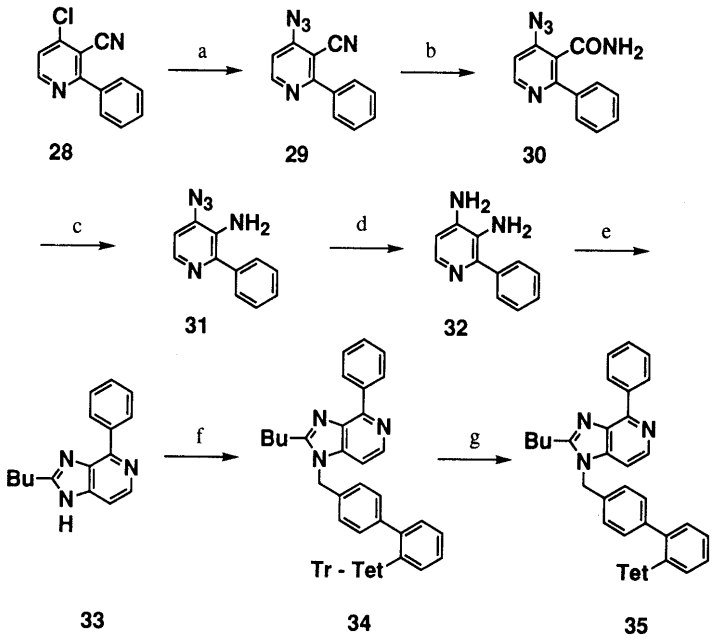
Chart 5. Preparation of the AII Antagonist **24**



25 26 27 28

reagents: (a) Ac_2O; (b) NH_3-MeOH; (c) $POCl_3$ / DMF / CH_2Cl_2

Chart 6. Preparation of the Chloropyridine Intermediate **28**



reagents: (a) NaN_3 / DMF; (b) conc. H_2SO_4; (c) Br_2 / NaOH / H_2O / CH_2Cl_2; (d) $SnCl_2 \cdot 2H_2O$ / NaOH / EtOH / THF; (e) *n*-Bu-CO_2H / PPA; (f) NaH / DMF; (g) conc.HCl / MeOH

Chart 7. Preparation of the AII Antagonist **35**

TABLE III. Physicochemical Data and *in Vitro* AII Antagonist Potencies of the AII Antagonists

Compound	R^1	R^2	mp (°C)	Formula[a]	K_i (nM)[b]	log P[c]
1a	Phenyl	*n*-Butyl	240—241	$C_{30}H_{27}N_7$	4.1	
1b	Phenyl	Ethyl	257—259	$C_{28}H_{23}N_7 \cdot 0.1H_2O$	8.0	
1c	Phenyl	*n*-Propyl	238—240	$C_{29}H_{25}N_7$	1.4	7.08
1d	Phenyl	Cyclopropyl	193—197	$C_{29}H_{23}N_7$	7.1	
1e	Phenyl	*n*-Pentyl	245—247	$C_{31}H_{29}N_7$	10.0	
1f	2-Cl-Phenyl	*n*-Propyl	Foam	$C_{29}H_{24}ClN_7$	1.1	7.80
1g	2-Cl-Phenyl	*n*-Butyl	201—203	$C_{30}H_{26}ClN_7$	1.4	
1h	3-CF_3-Phenyl	*n*-Propyl	199—201	$C_{30}H_{24}F_3N_7$	7.1	7.97
1i	Thiophen-2-yl	*n*-Propyl	244—246	$C_{27}H_{23}N_7S$	3.4	6.96
1j	Thiophen-2-yl	*n*-Butyl	233—235 (dec.)	$C_{28}H_{25}N_7S \cdot 1H_2O$	1.6	
1k	Furan-2-yl	*n*-Propyl	237—239	$C_{27}H_{23}N_7O$	5.9	6.47
1l[d]	H	*n*-Butyl			9.2	5.27
2a	Phenyl	*n*-Butyl	184—185	$C_{30}H_{27}N_7$	3.0	
2b	Phenyl	Ethyl	204—206	$C_{28}H_{23}N_7$	24.0	
2c	Phenyl	*n*-Propyl	183—185	$C_{29}H_{25}N_7$	6.8	7.08
2d	Phenyl	Cyclopropyl	165—167	$C_{29}H_{23}N_7$	8.7	
2e	Phenyl	*n*-Pentyl	193—195	$C_{31}H_{29}N_7$	25.0	
2f	2-Cl-Phenyl	*n*-Propyl	242—243 (dec.)	$C_{29}H_{24}ClN_7$	1.3	7.80
2g	2-Cl-Phenyl	*n*-Butyl	Foam	$C_{30}H_{26}ClN_7 \cdot 0.5H_2O$	1.5	
2h	3-CF_3-Phenyl	*n*-Propyl	215—217	$C_{30}H_{24}F_3N_7$	51.7	7.97
2i	Thiophen-2-yl	*n*-Propyl	250—255 (dec.)	$C_{27}H_{23}N_7S \cdot 0.25H_2O$	17.0	6.96
2j	Thiophen-2-yl	*n*-Butyl	220—221	$C_{28}H_{25}N_7S$	5.5	
2k	Furan-2-yl	*n*-Propyl	262—264	$C_{27}H_{23}N_7O$	3.0	6.47
2l[d]	H				3.0	5.27
24			Powder	$C_{30}H_{27}N_7$	190.0	
35			238—240	$C_{30}H_{27}N_7$	270.0	

a) Analytical results were within ±0.3% of the theoretical values. *b*) K_i values each represent an average of two or more determinations from separate assays. *c*) See ref. 11. *d*) Prepared according to ref. 5*f*.

Biological Results and Discussion

The compounds prepared above were evaluated as AII antagonists by testing the potency to displace [^{125}I]AII binding to COS cells transfected with a cDNA encoding a human AT_1 angiotensin II receptor. The K_i values calculated from IC_{50} values in this assay are listed in Table III.

First, the effect of the position of the aromatic substituent on the pyridine ring was examined using a series of 2-*n*-butyl derivatives (**1a**, **2a**, **24** and **35**). The 6-phenyl derivatives **1a** and **2a** showed receptor-binding affinity almost as potent as that of DuP 753 (K_i = 4.6 nM).

But, the 7- and 4-phenyl derivatives **24** and **35** showed poor binding affinity. Thus, the introduction of an aromatic substituent at the 7- or 4-position was presumed to be sterically unfavorable in the interaction with the AII receptor. The 1*H*-derivatives (**1a**, **c**, **f**—**j**) were equipotent to or more potent than the corresponding 3*H*-derivatives (**2a**, **c**, **f**—**j**), except for the furan-2-yl derivative (**1k**). The aromatic substituent of the 1*H*-derivatives may be better able to fit in the putative lipophilic pocket of the AII receptor.

Second, the effect of an alkyl chain at the 2-position was examined using a series of 6-phenyl derivatives (**1a**—**e**, **2a**—**e**). The *n*-propyl or *n*-butyl group was found to be the most appropriate for receptor-binding affinity among the alkyl groups we tested.

Finally, the effect of various aryl substituents at the 6-position was examined. The 3*H*-derivatives (**2a**, **c**, **f**—**k**) showed a wide range of K_i values (1.3—51.7 nM), whereas the 1*H*-derivatives (**1a**, **c**, **f**—**k**) showed a narrow range (1.1—7.1 nM). Therefore the binding affinity of the 3*H*-derivatives was strongly influenced by variation of the aromatic substituent at the 6-position. Although introduction of aromatic substituents did not always increase the receptor-binding affinity in comparison with the unsubstituted analogues **1l** and **2l**, the 6-(2-chlorophenyl)-imidazo[4,5-*c*]pyridine derivatives (**1f**—**g**, **2f**—**g**) possessed K_i values of about 1 nM, having 4-fold more potent binding affinity than that of DuP 753. A positive correlation between the binding affinity and CLOGP value[11] was observed in a series of the 2-propyl-1*H*-derivatives (**1c**, **f**, **i**, **k**). These results suggested that a lipophilic pocket is present in the AII receptor, and that the aromatic substituent on the imidazopyridine ring plays an effective role in the receptor binding. But the most lipophilic derivative **1h** showed only weak affinity. This undesirable result was attributed to the steric hindrance caused by the *meta*-substituent on the phenyl ring, which suggested that a steric factor was also important. A similar tendency was observed in a series of 2-propyl-3*H* derivatives (**2c**, **f**, **h**, **i**, **k**), but there was no clear correlation between the binding affinity and CLOGP value.

Some compounds showing high affinity in Table III were evaluated for oral antihypertensive activity in conscious spontaneously hypertensive rats (SHRs). DuP 753 (10 mg/kg, *p.o.*), which was used as a control compound, reduced the mean blood pressure (MBP) by more than 30 mmHg from the normal value at the maximum. Administration of **1c** (10 mg/kg) induced more than 20 mmHg reduction of MBP, but the lowering of the blood pressure was transient. Administration of 30 mg/kg of **1c** was required for the maximal effect, which was equal to that of DuP 753 (Fig. 3). Compound **1d** induced more than 40 mmHg reduction of MBP at 30 mg/kg but showed only weak activity at 10 mg/kg. Unexpectedly, **1f** and **2f**, which were the most potent in the binding assay, showed no antihypertensive activity at 10 mg/kg and only weak activity even at 30 mg/kg. Compounds **1g**—**k** also showed weak activity.

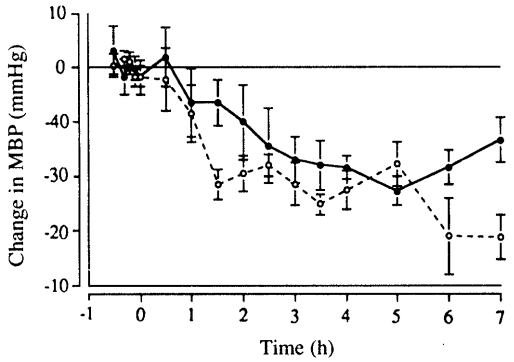


Fig. 3. Oral Antihypertensive Activity in Conscious SHR of **1c** (30 mg/kg, $n=3$, ●) and DuP 753 (10 mg/kg, $n=3$, ○)

Values represent the means ± SEM.

Conclusion

A series of 2-alkyl-6-arylimidazo[4,5-*c*]pyridine derivatives was synthesized and evaluated as novel potent AII receptor antagonists. Among the compounds with a variety of substituents at the 2- and 6-positions, the 6-(2-chlorophenyl)-2-*n*-propyl derivatives **1f** and **2f** were the most potent, showing *ca.* 4-fold more potent receptor-binding affinity than DuP 753. When administered orally, however, the series of compounds did not show strong or long-lasting antihypertensive activity comparable to that of DuP 753.

Experimental

General Procedures Melting points were determined on a Yanagimoto hot plate micro melting point apparatus without correction. Infrared (IR) spectra were recorded on a Hitachi 260-10 infrared spectrophotometer. ^{1}H-NMR spectra were recorded on a Varian VXR-200 spectrometer in $CDCl_3$ unless otherwise noted. Chemical shifts are reported as δ values with respect to tetramethylsilane (TMS) as an internal standard. Signal multiplicities are represented by s (singlet), d (doublet), t (triplet), q (quartet), br (broad), and m (multiplet). Abbreviations are as follows: Tet, tetrazole; Tr, trityl; TFA, trifluoroacetic acid. Column chromatography was done on Kieselgel 60 (E. Merck, 230—400 mesh). Organic extracts were dried over $MgSO_4$.

Ethyl 4-Oxo-6-phenyl-1,4-dihydropyridine-3-carboxylate (5a) Sodium hydride (6.75 g, 169 mmol; 60% dispersion in oil) washed with *n*-hexane (50 ml × 4) was suspended in tetrahydrofuran (THF) (240 ml). To the above stirred suspension was added dropwise a solution of ethyl 2-acetyl-3-aminoacrylate (**3**) (10.19 g, 65 mmol) in THF (90 ml) at −18 to −10 °C under nitrogen. The mixture was allowed to warm to room temperature, then ethyl benzoate (18.5 ml, 130 mmol) was added and the resulting mixture was refluxed with vigorous stirring for 1 h. The reaction mixture was then poured into concentrated HCl (18 ml) in ice water (500 ml). The mixture was made basic with saturated $NaHCO_3$. The organic layer was separated, then partitioned between EtOAc (300 ml) and H_2O (100 ml). All of the aqueous layers were combined and extracted with CH_2Cl_2 (200 ml × 3). The organic extract was concentrated *in vacuo*, and the residue was diluted with EtOAc (300 ml). The EtOAc layer was washed with H_2O and brine, dried and then concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel with *n*-hexane–EtOAc (v/v, 3/1) to give 6.76 g (43%) of **5a** as white crystals, mp 120—121 °C (*n*-hexane). ^{1}H-NMR ($CDCl_3$) δ: 1.48 (3H, t, $J=7.0$ Hz), 4.50 (2H, q, $J=7.0$ Hz), 7.35 (1H, s), 7.4—7.60 (3H, m), 7.95—8.10 (2H, m), 9.06 (1H, s). IR (Nujol): 1660, 1614, 1595, 1562 cm^{-1}. EI-MS *m/z*: 243 $(M)^+$. *Anal.* Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.14; H, 5.32; N, 5.84.

Ethyl 6-Aryl-4-oxo-1,4-dihydropyridine-3-carboxylate (5b—e) The preparation of **5b**—**e** was carried out according to the procedure for **5a**.

Ethyl 4-Chloro-6-phenylpyridine-3-carboxylate (6a) A mixture of compound **5a** (23.36 g, 96 mmol) and $POCl_3$ (44.8 ml, 0.481 mol) was refluxed for 1 h and concentrated *in vacuo*. The residual oil was poured into ice water (300 ml), and the aqueous solution was extracted with CH_2Cl_2 (100 ml × 3). The extract was washed successively with H_2O, saturated $NaHCO_3$, and brine, and then dried. Removal of the solvent

TABLE IV. Physicochemical Data for **5b—e**

Compd.	Analysis (%) Calcd (Found)	^{1}H-NMR ($CDCl_3$)
5b	C: 60.55 (60.60) H: 4.36 (4.44) Cl: 12.77 (13.05) N: 5.04 (5.12)	1.46 (3H, t, J=7.0 Hz), 4.49 (2H, q, J=7.0 Hz), 7.26 (1H, s), 7.34—7.62 (4H, m), 9.06 (1H, s)
5c	C: 57.88 (57.77) H: 3.89 (4.03) F: 18.31 (18.11) N: 4.50 (4.62)	1.47 (3H, t, J=7.4 Hz), 4.49 (2H, q, J=7.4 Hz), 7.36 (1H, s), 7.61 (1H, t, J=7.6 Hz), 8.32 (1H, s), 9.05 (1H, s)
5d	C: 57.82 (57.73) H: 4.55 (4.50) N: 5.62 (5.57) S: 12.86 (12.61)	1.44 (3H, t, J=7.0 Hz), 4.45 (2H, q, J=7.0 Hz), 7.13 (1H, dd, J=5.0, 3.6 Hz), 7.22 (1H, s), 7.48 (1H, dd, J=5.0, 1.2 Hz), 7.64 (1H, dd, J=3.6, 1.2 Hz), 8.91 (1H, s)
5e	C: 61.80 (61.84) H: 4.75 (4.81) N: 6.01 (6.08)	1.44 (3H, t, J=7.2 Hz), 4.46 (2H, q, J=7.2 Hz), 6.56 (1H, dd, J=3.6, 1.8 Hz), 7.14 (1H, dd, J=3.6, 0.8 Hz), 7.27 (1H, s), 7.57 (1H, dd, J=1.8, 0.8 Hz), 8.93 (1H, d, J=0.4 Hz)

in vacuo, gave crude crystals of **6a** (24.91 g, 99%). ^{1}H-NMR ($CDCl_3$) δ: 1.43 (3H, t, J=7 Hz), 4.42 (2H, q, J=7 Hz), 7.36—7.60 (3H, m), 7.80 (1H, s), 7.90—8.15 (2H, m), 9.11 (1H, s).

Ethyl 4-Azido-6-phenylpyridine-3-carboxylate (7a) A suspension of **6a** (24.91 g, 95.2 mmol) and NaN_3 (19.3 g, 0.288 mol) in DMF (265 ml) was heated at 70 °C for 2 h under nitrogen. The resulting inorganic salt was filtered off and washed thoroughly with EtOAc. The filtrate was concentrated *in vacuo*. The residue was partitioned between EtOAc (100 ml) and H_2O (300 ml), and the aqueous layer was further extracted with EtOAc (100 ml × 2). The organic extract was washed with H_2O, and brine, then dried. Removal of the solvent gave a crude product, which was purified by column chromatography on silica gel with *n*-hexane–EtOAc (v/v, 6/1), affording 18.63 g (72.3%) of **7a** as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.42 (3H, t, J=7.0 Hz), 4.42 (2H, q, J=7.0 Hz), 7.45—7.58 (4H, m), 7.96—8.05 (2H, m), 9.01 (1H, s). IR ($CHCl_3$) 2100, 1720, 1590, 1545, 1140, 1095 cm^{-1}.

4-Azido-6-phenylpyridine-3-carboxylic Acid (8a) A solution of KOH (7.78 g, 139 mmol) in H_2O (43 ml) was added dropwise to a stirred solution of **7a** (18.63 g, 69.5 mmol) in EtOH (394 ml) at 0 °C, and the mixture was allowed to warm to room temperature. It was stirred for 1 h, then concentrated *in vacuo*. The remaining salt was dissolved in H_2O (100 ml) and the solution was made acidic with 1 N HCl (150 ml), while the liberated acid precipitated. After 30 min at room temperature, the crystals were collected by filtration, washed with H_2O, then dried under reduced pressure for 12 h to give 16 g (95.8%) of **8a** as a colorless solid. ^{1}H-NMR (DMSO-d_6) δ: 7.45—7.65 (3H, m), 7.84 (1H, s), 8.10—8.30 (2H, m), 8.97 (1H, s). IR (Nujol): 2120, 1710, 1550, 1260, 1235 cm^{-1}. MS *m/z*: 240 (M^+).

4-Azido-3-[*N*-(*tert*-butyloxycarbonyl)amino]-6-phenylpyridine (9a) A solution of $ClCO_2Et$ (7.96 g, 73.3 mmol) in THF (30 ml) was added to a solution of **8a** (16.0 g, 66.7 mmol) and Et_3N (7.41 g, 73.3 mmol) in THF (420 ml) at −10 °C and the mixture was stirred for 30 min at the same temperature. A solution of NaN_3 (22.35 g, 333.5 mmol) in H_2O (160 ml) was then added at −10 to −3 °C. The mixture was stirred vigorously at room temperature for 1 h. The resulting precipitate was filtered off and washed with THF. The filtrate was concentrated *in vacuo* and the residue was diluted with H_2O (500 ml). The crystals were collected by filtration, washed with H_2O, and dissolved in CH_2Cl_2. The organic solution was washed with brine, dried, then concentrated *in vacuo* to give crude crystals of the acylazide. A solution of the crystals in *tert*-BuOH (160 ml) and 1,2-dichloroethane (380 ml) was refluxed for 1 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatography on silica gel with *n*-hexane–EtOAc (v/v, 5/1) to afford 16.84 g (81.1%) of **9a** as white crystals, mp 119—120 °C (*n*-hexane). ^{1}H-NMR ($CDCl_3$) δ: 1.54 (9H, s), 6.67 (1H, br s), 7.37—7.50 (4H, m), 7.85—7.98 (2H, m), 9.30 (1H, s). IR (Nujol): 3270, 3150, 2115, 1715, 1590 cm^{-1}. MS *m/z*: 311 (M^+). *Anal.* Calcd for $C_{16}H_{17}N_5O_2$: C, 61.72; H, 5.50; N, 22.49. Found: C, 62.00; H, 5.65; N, 22.41.

4-Amino-3-[*N*-(tert-butyloxycarbonyl)amino]-6-phenylpyridine (10a) A solution of $SnCl_2 \cdot 2H_2O$ (19.75 g, 87.5 mmol) in 2 N NaOH (277 ml) was added to a stirred solution of **9a** (19.44 g, 62.5 mmol) in EtOH (370 ml) and THF (55 ml) at 0 to 8 °C over 15 min. Nitrogen gas evolved throughout the addition. The reaction mixture was stirred for 30 min at room temperature, and filtered through a Celite pad. The filtrate was concentrated *in vacuo*, and the residue was partitioned between EtOAc (150 ml) and H_2O (500 ml). The aqueous layer was further extracted with EtOAc (100 ml × 3). The organic extract was washed with H_2O and brine, then dried. Removal of the solvent afforded crude crystals of **10a** (17.8 g, quant.), mp 166—168 °C (EtOAc). ^{1}H-NMR ($CDCl_3$) δ: 1.51 (9H, s), 4.54 (2H, br s), 6.39 (1H, br s), 7.00 (1H, s), 7.30—7.46 (3H, m), 7.80—7.90 (2H, m), 8.24 (1H, s). IR ($CHCl_3$): 3420, 2975, 1710, 1625, 1490, 1370, 1160 cm^{-1}. *Anal.* Calcd for $C_{16}H_{19}N_3O_2$: C, 67.35; H, 6.71; N, 14.73. Found: C, 67.43; H, 6.62; N, 14.62.

2-*n*-Butyl-6-phenyl-1*H*-imidazo[4,5-*c*]pyridine (11a) A suspension of **10a** (1.43 g, 5 mmol) and valeric acid (610 mg, 5.97 mmol) in polyphosphoric acid (3 ml) was heated at 130 °C for 6 h under nitrogen. The reaction mixture was then poured into ice water. The mixture was made basic with NH_4OH and extracted with $CHCl_3$ (20 ml × 2). The organic extract was washed with H_2O and brine, then dried. Removal of the solvent afforded crude crystals of **11a** (1.13 g, 89.9%), mp 191—193 °C (EtOAc). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=7.2 Hz), 1.30—1.50 (2H, m), 1.75—1.92 (2H, m), 2.80 (2H, t, J=7.8 Hz), 5.28 (2H, s), 6.80—7.00 (8H, m), 7.05—7.55 (17H, m), 7.90—8.05 (3H, m), 8.10 (1H, s), 8.61 (1H, s). *Anal.* Calcd for $C_{16}H_{17}N_3$: C, 76.46; H, 6.82; N, 16.72. Found: C, 76.66; H, 6.80; N, 16.85.

2-Alkyl-6-aryl-1*H*-imidazo[4,5-*c*]pyridine (11b—k) The preparation of **11b—k** was carried out according to the procedure described for **11a**.

2-*n*-Butyl-6-phenyl-1-[[2′-(2-trityl-2*H*-tetrazol-5-yl)biphenyl-4-yl]-methyl]-1*H*-imidazo[4,5-*c*]pyridine (12a) and 2-*n*-Butyl-6-phenyl-3-[[2′-(2-trityl-2*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-3*H*-imidazo[4,5-*c*]-pyridine (13a) Sodium hydride (50 mg, 1.25 mmol; 60% dispersion in oil) washed with *n*-hexane (5 ml × 4) was suspended in DMF (6 ml). To the above stirred suspension was added **11a** (190 mg, 0.76 mmol) at −20 °C under nitrogen. The mixture was allowed to warm to room temperature and stirred for 10 min, then 5-(4′-bromomethylbiphenyl-2-yl)-2-trityl-2*H*-tetrazole (530 mg, 83.34%, 0.79 mmol) was added and the resulting mixture was stirred for 3 h. The reaction mixture was then poured into ice water. The mixture was extracted with EtOAc (20 ml × 2). The organic extract was washed with H_2O and brine, then dried. The crude product was purified by column chromatography on silica gel with *n*-hexane–EtOAc (v/v, 1/1) to give 290 mg (52.4%) of **12a** and 140 mg (25.3%) of **13a** as white crystals. **12a**: ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, t, J=7.2 Hz), 1.30—1.50 (2H, m), 1.75—1.95 (2H, m), 2.76 (2H, t, J=7.4 Hz), 5.26 (2H, s), 6.75—6.92 (8H, m), 7.05—7.50 (18H, m), 7.82—7.96 (3H, m), 9.16 (1H, d, J=0.6 Hz). **13a**: ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.2 Hz), 1.30—1.50 (2H, m), 1.75—1.92 (2H, m), 2.80 (2H, t, J=7.8 Hz), 5.28 (2H, s), 6.80—7.00 (8H, m), 7.05—7.55 (17H, m), 7.90—8.05 (3H, m), 8.10 (1H, s), 8.61 (1H, s).

2-*n*-Butyl-6-phenyl-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-imidazo[4,5-*c*]pyridine (1a) A suspension of **12a** (290 mg, 0.4 mmol) in MeOH (3 ml) was treated with 0.2 ml of concentrated HCl. The reaction mixture was stirred at room temperature for 10 min, and concentrated *in vacuo*. The residue was diluted with H_2O and neutralized with aqueous $NaHCO_3$. The aqueous solution was extracted with CH_2Cl_2 (20 ml × 2). The organic extract was washed with H_2O and brine, then dried. Removal of the solvent afforded crude crystals of **1a** (150 mg, 77.5%), mp 240—241 °C (MeOH). ^{1}H-NMR ($CDCl_3+CD_3OD$) δ: 0.95 (3H, t, J=7.2 Hz), 1.35—1.52 (2H, m), 1.72—1.90 (2H, m), 2.88 (2H, t, J=7.4 Hz), 5.43 (2H, s), 7.00 and 7.12 (2H × 2, ABq, J=8.4 Hz), 7.35—7.70 (8H, m), 7.82—7.90 (2H, m), 8.99 (1H, d, J=0.8 Hz). *Anal.* Calcd for $C_{30}H_{27}N_7$: C, 74.20; H, 5.60; N, 20.19. Found: C, 74.08; H, 5.63; N, 20.15.

2-Alkyl-6-aryl-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-imidazo[4,5-*c*]pyridine (1b—k) The preparation of **1b—k** was carried out according to the procedure described for **1a**.

2-*n*-Butyl-6-phenyl-3-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-3*H*-imidazo[4,5-*c*]pyridine (2a) The deprotection of **13a** (140 mg, 0.19

TABLE V. Physicochemical Data for **11b—k**

Compd.	Analysis (%) Calcd (Found)	^{1}H-NMR ($CDCl_3$)
11b	C : 75.31 (75.37) H: 5.87 (5.98) N : 18.82 (18.77)	1.45 (3H, t, J=7.6 Hz), 2.99 (2H, q, J=7.6 Hz), 7.36—7.54 (3H, m), 7.80—7.96 (3H, m), 8.82 (1H, s)
11c	C : 75.92 (76.03) H: 6.37 (6.41) N : 17.71 (17.67)	1.04 (3H, t, J=7.2 Hz), 1.81—2.00 (2H, m), 2.94 (2H, t, J=7.4 Hz), 7.32—7.58 (3H, m), 7.84—7.95 (3H, m), 8.82 (1H, d, J=0.8 Hz)
11d	C : 76.57 (76.76) H: 5.57 (5.58) N : 17.86 (17.80)	1.10—1.28 (4H, m), 2.05—2.22 (1H, m), 7.37—7.54 (3H, m), 7.77 (1H, s), 7.82—7.94 (2H, m), 8.78 (1H, s)
11e	C : 76.95 (76.90) H: 7.22 (7.17) N : 15.84 (15.77)	1.18—1.40 (4H, m), 1.75—1.95 (2H, m), 2.91 (2H, t, J=7.4 Hz), 7.27—7.40 (3H, m), 7.72 (1H, s), 7.80—7.90 (2H, m), 8.85 (1H, d, J=0.6 Hz)
11f	C : 66.30 (66.32) H: 5.19 (5.23) Cl: 13.05 (12.83) N: 15.46 (15.43)	1.72—1.90 (2H, m), 2.82 (2H, t, J=7.2 Hz), 7.22—7.30 (2H, m), 7.36—7.42 (1H, m), 7.50—7.56 (1H, m), 7.63 (1H, s), 8.90 (1H, s)
11g	C : 67.25 (67.07) H: 5.64 (5.73) Cl: 12.41 (12.71) N: 14.70 (14.56)	0.87 (3H, t, J=7.4 Hz), 1.24—1.42 (2H, m), 1.70—1.85 (2H, m), 2.84 (2H, t, J=7.4 Hz), 7.20—7.58 (4H, m), 7.61 (1H, s), 8.89 (1H, s)
11h	C : 62.94 (63.12) H: 4.62 (4.67) F : 18.67 (18.68) N: 13.76 (13.72)	1.02 (3H, t, J=7.0 Hz), 1.84—2.00 (2H, m), 2.95 (2H, t, J=7.4 Hz), 7.50—7.64 (2H, m), 7.81 (1H, s), 8.11 (1H, d, J=7.0 Hz), 8.22 (1H, s), 8.99 (1H, s)
11i	C : 64.17 (64.19) H: 5.39 (5.45) N : 17.27 (17.17) S: 13.18 (13.22)	0.99 (3H, t, J=7.4 Hz), 1.80—1.98 (2H, m), 2.91 (2H, t, J=7.6 Hz), 7.06 (1H, dd, J=5.2, 3.8 Hz), 7.30 (1H, dd, J=5.2, 1.0 Hz), 7.45 (1H, dd, J=3.8, 1.0 Hz), 7.74 (1H, d, J=0.8 Hz), 8.80 (1H, d, J=0.8 Hz)
11j	C : 65.34 (65.52) H: 5.87 (5.92) N : 16.33 (16.42) S: 12.46 (12.63)	0.96 (3H, t, J=7.2 Hz), 1.38—1.56 (2H, m), 1.80—1.96 (2H, m), 2.95 (2H, t, J=7.8 Hz), 7.10 (1H, dd, J=5.0, 3.6 Hz), 7.34 (1H, dd, J=5.0, 1.2 Hz), 7.53 (1H, dd, J=3.6, 1.2 Hz), 7.77 (1H, d, J=0.8 Hz), 8.86 (1H, d, J=0.8 Hz)
11k	C : 68.70 (68.87) H: 5.77 (5.73) N : 18.49 (18.60)	1.00 (3H, t, J=7.4 Hz), 1.80—2.00 (2H, m), 2.94 (2H, t, J=7.2 Hz), 6.49 (1H, dd, J=3.2, 1.6 Hz), 6.95 (1H, dd, J=3.2, 0.8 Hz), 7.45 (1H, dd, J=1.6, 0.8 Hz), 7.82 (1H, d, J=0.8 Hz), 8.87 (1H, s)

TABLE VI. Physicochemical Data for **1b—k**

Compd.	Analysis (%) Calcd (Found)	^{1}H-NMR ($CDCl_3$)
1b	C : 73.10 (73.22) H: 5.28 (5.09) N : 21.27 (21.35)	1.36 (3H, t, J=7.4 Hz), 2.82 (2H, q, J=7.4 Hz), 5.38 (2H, s), 6.94 and 7.08 (2H×2, ABq, J=8.2 Hz), 7.34—7.85 (10H, m), 8.90 (1H, s)
1c	C : 73.86 (73.80) H: 5.34 (5.50) N : 20.79 (20.66)	1.04 (3H, t, J=7.4 Hz), 1.80—1.95 (2H, m), 2.86 (2H, t, J=7.8 Hz), 5.43 (2H, s), 7.00 and 7.13 (2H×2, ABq, J=8.4 Hz), 7.35—7.70 (9H, m), 7.80—7.90 (2H, m), 8.99 (1H, d, J=0.8 Hz)
1d	C : 70.14 (70.32) H: 5.28 (4.99) N : 19.75 (19.82)	1.18—1.35 (4H, m), 1.95—2.10 (1H, m), 5.63 (2H, s), 7.05—7.18 (4H, m), 7.36—7.85 (7H, m), 7.80—7.95 (3H, m), 8.90 (1H, s)
1e	C : 74.53 (74.63) H: 5.85 (5.99) N : 19.62 (19.47)	0.85—0.95 (3H, m), 1.25—1.50 (4H, m), 1.75—1.95 (2H, m), 2.91 (2H, t, J=7.6 Hz), 5.51 (2H, s), 7.01 and 7.13 (2H×2, ABq, J=8.4 Hz), 7.40—7.75 (7H, m), 7.78 (1H, s), 7.82—7.95 (2H, m), 9.03 (1H, s)
1f	C : 66.93 (67.19) H: 4.96 (4.93) Cl: 6.81 (6.45) N: 18.84 (18.67)	0.93 (3H, t, J=7.2 Hz), 1.65—1.92 (2H, m), 2.67 (2H, t, J=7.2 Hz), 5.21 (2H, s), 6.65—6.90 (4H, m), 7.15—7.75 (9H, m), 8.57 (1H, d, J=0.6 Hz)
1g	C : 69.29 (69.57) H: 5.04 (5.19) Cl: 6.82 (6.67) N: 18.85 (18.82)	0.90 (3H, t, J=7.4 Hz), 1.30—1.50 (2H, m), 1.68—1.84 (2H, m), 2.74 (2H, t, J=7.4 Hz), 5.30 (2H, s), 6.72 and 6.90 (2H×2, ABq, J=8.0 Hz), 7.05—7.75 (10H, m), 8.45 (1H, s)
1h	C : 66.78 (66.98) H: 4.48 (4.65) F : 10.56 (10.34) N: 18.17 (18.15)	1.03 (3H, t, J=7.4 Hz), 1.78—1.96 (2H, m), 2.84 (2H, t, J=7.8 Hz), 5.45 (2H, s), 6.99 and 7.13 (2H×2, ABq, J=8.4 Hz), 7.40—7.70 (7H, m),8.04—8.16 (1H, m), 8.19 (1H, d, J=1.6 Hz), 9.04 (1H, d, J=1.0 Hz)
1i	C : 67.90 (67.87) H: 4.85 (4.94) N : 20.53 (20.31) S: 6.71 (6.58)	1.03 (3H, t, J=7.6 Hz), 1.78—1.94 (2H, m), 2.82 (2H, t, J=7.2 Hz), 5.40 (2H, s), 6.97—7.18 (5H, m), 7.30—7.75 (7H, m), 8.92 (1H, d, J=1.0 Hz)
1j	C : 65.99 (65.69) H: 5.34 (5.16) N : 19.24 (19.18) S: 6.29 (6.01)	0.94 (3H, t, J=7.2 Hz), 1.35—1.50 (2H, m), 1.70—1.85 (2H, m), 2.83 (2H, t, J=7.4 Hz), 5.36 (2H, s), 6.90—7.16 (5H, m), 7.34—7.62 (7H, m), 8.89 (1H, d, J=0.8 Hz)
1k	C : 70.27 (70.38) H: 5.02 (5.16) N : 21.24 (21.09)	1.02 (3H, t, J=7.4 Hz), 1.75—1.98 (2H, m), 2.81 (2H, t, J=7.4 Hz), 5.38 (2H, s), 6.54 (1H, dd, J=3.4, 1.8 Hz), 6.92—7.16 (5H, m), 7.42—7.75 (6H, m), 8.84 (1H, s)

mmol) was carried out according to the procedure described for **1a** to give 85 mg (91.0%) of **2a** as crude crystals, mp 184—185 °C (MeOH). ^{1}H-NMR ($CDCl_3$+CD_3OD) δ: 0.97 (3H, t, J=7.2 Hz), 1.40—1.60 (2H, m), 1.78—1.95 (2H, m), 2.95 (2H, t, J=7.4 Hz), 5.43 (2H, s), 7.04 and 7.15 (2H×2, ABq, J=7.4 Hz), 7.36—7.60 (6H, m), 7.70—7.95 (3H, m), 7.99 (1H, s), 8.40 (1H, s). *Anal.* Calcd for $C_{30}H_{27}N_7$: C, 74.20; H, 5.60; N, 20.19. Found: C, 74.17; H, 5.63; N, 20.13.

2-Alkyl-6-aryl-3-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-3*H*-imidazo[4,5-*c*]pyridine (2b—k) The preparation of **2b—k** was carried out according to the procedure described for **1a**.

Methyl 4-Oxo-5-phenyl-1,4-dihydropyridine-3-carboxylate (14) A mixture of methyl 3-oxo-5-phenylbutylate (13.22 g, 68.8 mmol) and DMF dimethylacetal (22.4 g, 188 mmol) in xylene (120 ml) was heated at 120 °C with removal of the MeOH for 2 h and then concentrated *in vacuo*. The residue in MeOH (150 ml) was treated with NH_4OAc (27 g) and the mixture was refluxed for 1.5 h. The precipitate was collected by filtration and successively washed with MeOH, H_2O and MeOH to give 9.24 g (58.6%) of **14**, which was used for the next reaction without further purification. IR (Nujol): 1705, 1640, 1595 cm^{-1}.

Methyl 4-Azido-5-phenylpyridine-3-carboxylate (15) A suspension of **14** (7.62 g, 33.2 mmol) in $POCl_3$ (15 ml) was heated at reflux for 1 h and concentrated *in vacuo*. The residue was partitioned between EtOAc and ice water. The organic layer was washed with H_2O and brine, then dried. The solvent was removed to afford the crude 4-chloropyridine, which was dissolved in DMF (80 ml) containing NaN_3 (6.68 g, 102 mmol). The DMF suspension was heated at 95 °C for 30 min and concentrated

TABLE VII. Physicochemical Data for **2b—k**

Compd.	Analysis (%) Calcd (Found)	^{1}H-NMR ($CDCl_3$)
2b	C : 73.50 (73.60) H: 5.07 (5.15) N : 21.43 (21.41)	1.35 (3H, t, J=7.4 Hz), 2.84 (2H, q, J=7.4 Hz), 6.90 and 6.98 (2H×2, ABq, J=8.2 Hz), 7.24—7.50 (6H, m), 7.75—7.82 (4H, m), 8.48 (1H, s)
2c	C : 73.86 (73.80) H: 5.34 (5.50) N : 20.79 (20.66)	1.00 (3H, t, J=7.0 Hz), 1.70—1.95 (2H, m), 2.76 (2H, t, J=7.2 Hz), 5.25 (2H, s), 6.80—7.00 (4H, m), 7.22—7.50 (7H, m), 7.70—7.90 (4H, m), 8.39 (1H, d, J=1.4 Hz)
2d	C : 71.99 (71.85) H: 5.34 (5.31) N : 18.96 (19.20)	1.22—1.40 (4H, m), 2.00—2.15 (1H, m), 5.53 (2H, s), 7.10—7.18 (4H, m), 7.40—7.60 (6H, m), 7.80—7.95 (4H, m), 8.30 (1H, s)
2e	C : 74.53 (74.62) H: 5.85 (6.01) N : 19.62 (19.50)	0.86—1.00 (3H, m), 1.30—1.55 (4H, m), 1.84—2.00 (2H, m), 2.89 (2H, t, J=7.6 Hz), 5.43 (2H, s), 7.17 and 7.09 (2H×2, ABq, J=6.6 Hz), 7.40—7.60 (6H, m), 7.80—7.95 (3H, m), 8.00 (1H, d, J=0.8 Hz), 8.31 (1H, s)
2f	C : 68.84 (68.99) H: 4.78 (4.71) Cl: 7.01 (6.80) N: 19.38 (19.26)	1.10 (3H, t, J=7.4 Hz), 1.85—2.02 (2H, m), 2.98 (2H, t, J=7,2 Hz), 5.45 (2H, s), 7.04—7.20 (4H, m), 7.30—7.60 (6H, m), 7.82—7.90 (1H, m), 7.87 (1H, s), 8.32 (1H, d, J=0.8 Hz)
2g	C : 68.11 (68.12) H: 5.14 (5.07) Cl: 6.70 (6.75) N: 18.53 (18.43)	0.94 (3H, t, J=7.4 Hz), 1.35—1.58 (2H, m), 1.76—1.90 (2H, m), 2.91 (2H, t, J=7.2 Hz), 5.41 (2H, s), 6.88 and 6.98 (2H×2, ABq, J=8.2 Hz), 7.20—7.50 (8H, m), 7.75—7.82 (2H, m), 8.64 (1H, s)
2h	C : 66.78 (66.96) H: 4.48 (4.64) F : 10.56 (10.33) N: 18.17 (18.18)	1.08 (3H, t, J=7.4 Hz), 1.82—2.05 (2H, m), 2.95 (2H, t, J=7.6 Hz), 5.45 (2H, s), 7.05 and 7.14 (2H×2, ABq, J=8.6 Hz), 7.40—7.70 (5H, m), 7.80—7.86 (1H, m), 8.01 (1H, d, J=7.4 Hz), 8.20 (1H, s), 8.43 (1H, d, J=0.6 Hz)
2i	C : 67.27 (67.39) H: 4.91 (5.01) N : 20.34 (20.09) S: 6.65 (6.49)	1.08 (3H, t, J=7.4 Hz), 1.84—2.00 (2H, m), 2.93 (2H, t, J=7.4 Hz), 5.42 (2H, s), 7.00—7.20 (5H, m), 7.32—7.62 (5H, m), 7.80—7.90 (1H, m), 7.98 (1H, s), 8.33 (1H, s)
2j	C : 68.41 (68.47) H: 5.13 (5.04) N : 19.94 (19.78) S: 6.52 (6.34)	0.95 (3H, t, J=7.2 Hz), 1.38—1.55 (2H, m), 1.75—1.90 (2H, m), 2.82 (2H, t, J=7.4 Hz), 5.31 (2H, s), 7.00—7.18 (5H, m), 7.32—7.46 (2H, m), 7.50—7.60 (3H, m), 7.74 (1H, s), 8.00—8.08 (1H, m), 8.11 (1H, s)
2k	C : 70.27 (69.93) H: 5.02 (5.24) N : 21.24 (20.94)	1.06 (3H, t, J=7.4 Hz), 1.80—2.00 (2H, m), 2.92 (2H, t, J=7.2 Hz), 5.49 (2H, s), 6.56 (1H, dd, J=3.4, 1.8 Hz), 7.00—7.20 (5H, m), 7.42—7.78 (5H, m), 8.03 (1H, d, J=0.8 Hz), 8.48 (1H, d, J=0.8 Hz)

in vacuo. The residue was purified by chromatography on silica gel. Elution with *n*-hexane–EtOAc (v/v, 1/1) afforded 6.92 g (82%) of oily product **15**. ^{1}H-NMR ($CDCl_3$) δ: 4.01 (3H, s), 7.40—7.55 (5H, m), 8.57 (1H, s), 8.97 (1H, s). IR (film): 2100, 1715 cm^{-1}.

4-Azido-5-phenylpyridine-3-carboxylic Acid (16) A stirred solution of **15** (20.95 g, 82.4 mmol) in MeOH (180 ml) was treated with a solution of KOH (9.23 g, 164.8 mmol) in H_2O (20 ml) at 0 °C. The reaction mixture was gradually warmed to 20 °C. After having been stirred for 1 h, the mixture was concentrated *in vacuo* and a solution of the residue in H_2O was acidified with 1 N HCl (180 ml). The resulting precipitate was collected by filtration, and washed several times with H_2O, and then dried *in vacuo* to afford 19.1 g (96.5%) of **16**. ^{1}H-NMR (DMSO-d_6) δ: 7.50—7.60 (5H, s), 8.59 (1H, s), 8.91 (1H, s). IR (Nujol): 2130, 1700 cm^{-1}.

4-Azido-3-[*N*-(*tert*-butyloxycarbonyl)amino]-5-phenylpyridine (17) The preparation of **17** was carried out according to the procedure described for **9**. ^{1}H-NMR ($CDCl_3$) δ: 1.55 (9H, s), 6.95 (1H, br s), 7.40—7.55 (5H, m), 8.17 (1H, s), 9.23 (1H, s). IR (film): 3420, 3150, 2100, 1710 cm^{-1}.

2-*n*-Butyl-7-phenyl-3*H*-imidazo[4,5-*c*]pyridine (18) Compound **18** was derived from **17** according to the procedure described for **10** and **11**. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, J=7.2 Hz), 1.30—1.50 (2H, m), 1.75—1.95 (2H, m), 2.95 (2H, t, J=7.8 Hz), 7.25—7.45 (3H, m), 7.60—7.75 (17H, m), 8.34 (1H, s), 8.82 (1H, s).

2-*n*-Butyl-7-phenyl-5-[[2′-(2-trityl-2*H*-tetrazol-5-yl)biphenyl-4-yl]-methyl]-5*H*-imidazo[4,5-*c*]pyridine (19) The preparation of **19** was carried out according to the procedure described for **12**. ^{1}H-NMR ($CDCl_3$) δ: 0.98 (3H, t, J=7.2 Hz), 1.40—1.60 (2H, m), 1.85—2.05 (2H, m), 3.11 (2H, t, J=7.9 Hz), 5.34 (2H, s), 6.80—7.00 (8H, m), 7.10—7.55 (17H, m), 7.68 (1H, d, J=1.4 Hz), 7.85—8.00 (3H, m), 8.39 (1H, d, J=1.4 Hz).

2-*n*-Butyl-7-phenyl-5-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-5*H*-imidazo[4,5-*c*]pyridine (20) The preparation of **20** was carried out according to the procedure described for **1**. ^{1}H-NMR ($CDCl_3$) δ: 0.80 (3H, t, J=7.4 Hz), 1.18—1.35 (2H, m), 1.62—1.82 (2H, m), 2.88 (2H, t, J=7.8 Hz), 5.68 (2H, d, J=0.8 Hz), 6.87 and 7.15 (2H×2, ABq, J=7.8 Hz), 7.20—7.40 (6H, m), 7.60—7.75 (2H, m), 8.65 (1H, s), 9.33 (1H, s).

4′-[4-Azido-5-phenylpyridin-3-yl-*N*-(*tert*-butyloxycarbonyl)aminomethyl]biphenyl-2-carbonitrile (21) The preparation of **21** was carried out according to the procedure described for **12**. ^{1}H-NMR ($CDCl_3$) δ: 1.47 (9H, s), 4.62 (1H, br s), 5.02 (1H, br s), 7.40—7.72 (12H, m), 7.77 (1H, dd, J=7.4, 0.8 Hz), 8.15 (1H, br s), 8.36 (1H, s).

4′-[4-Amino-5-phenylpyridin-3-yl-*N*-(*tert*-butyloxycarbonyl)aminomethyl]biphenyl-2-carbonitrile (22) The preparation of **22** was carried out according to the procedure described for **10**. ^{1}H-NMR ($CDCl_3$) δ: 1.45 (9H, s), 4.20—4.30 (2H, m), 4.75—4.82 (2H, m), 7.30—7.80 (13H, m), 7.97—8.00 (1H, m), 8.08 (1H, s). IR (film): 3570, 3340, 2220, 1695, 1614 cm^{-1}.

4′-[(2-*n*-Butyl-7-phenylimidazo[4,5-*c*]pyridin-3-yl)methyl]biphenyl-2-carbonitrile (23) A stirred solution of **22** (2.85 g, 5.98 mmol) in CH_2Cl_2 (30 ml) was treated with TFA (4 ml) at 0 to 5 °C. The reaction mixture was stirred for 1 h at room temperature, and concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (30 ml) and aqueous $NaHCO_3$ (30 ml), and the aqueous layer was further extracted with CH_2Cl_2 (10 ml × 2). The organic extract was washed with H_2O and brine, then dried. The residue was dissolved in trimethyl ortho-*n*-valerate (10 ml), then AcOH (60 mg, 1 mmol) was added. Stirring was continued for 3 h at 100 °C, then the reaction mixture was concentrated *in vacuo*. The residue was partitioned between EtOAc (30 ml) and H_2O (30 ml), and the aqueous layer was further extracted with EtOAc (10 ml × 2). The organic extract was washed with H_2O and brine, then dried. The crude product was purified by column chromatography on silica gel with CH_2Cl_2–EtOAc (v/v, 3/1) to give 1.80 g (64%) of **23** as a foam. ^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, t. J=7.2 Hz), 1.40—1.58 (2H, m), 1.75—1.95 (2H, m), 2.96 (2H, t, J=7.4 Hz), 5.51 (2H, s), 7.18—7.25 (2H, m), 7.38—7.80 (9H, m), 8.04—8.10 (2H, m), 8.60 (1H, s), 8.62 (1H, s).

2-*n*-Butyl-7-phenyl-3-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-3*H*-imidazo[4,5-*c*]pyridine (24) A suspension of **23** (440 mg, 1 mmol) and trimethyltinazide (410 mg, 2 mmol) in xylene (10 ml) was stirred at 120 °C for 24 h under nitrogen. The reaction mixture was concentrated *in vacuo*, and the residue was suspended in EtOH (10 ml). This suspension was treated with 1 N HCl (4 ml), and the reaction mixture was stirred for 15 min at room temperature. After removal of the solvent, the residue was partitioned between EtOAc and ice water. The aqueous layer was extracted with EtOAc (10 ml × 2). The combined organic layer was dried and concentrated *in vacuo*. The residue was purified by chromatography on silica gel. Elution with $CHCl_3$–MeOH (v/v, 8/1) afforded 380 mg (78%) of **24** as a powder. ^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, t, J=7.2 Hz), 1.20—1.38 (2H, m), 1.80—1.95 (2H, m), 3.00 (2H, t, J=7.8 Hz), 5.44 (2H, s), 6.69 and 6.83 (2H×2, ABq, J=8.0 Hz), 7.20—7.28 (1H, m), 7.35—7.58 (5H, m), 7.85—7.90 (1H, m), 7.95—8.03 (2H, m), 8.42 (1H, s), 8.94 (1H, s). *Anal.* Calcd for $C_{30}H_{27}N_7 \cdot 0.6H_2O$: C, 72.59; H, 5.73; N, 19.75. Found: C, 72.67; H, 5.60; N, 19.51.

2-Acetyl-3-ethoxy-3-phenylacrylonitrile (25) A mixture of 3-oxobu-

tyronitrile (10.4 g, 125 mmol), triethyl orthobenzoate (28 g, 125 mmol) and Ac_2O (23.6 ml) was gradually heated to 130 °C and stirred for 3 h. It was then concentrated *in vacuo* and the residue was partitioned between EtOAc and aqueous $NaHCO_3$. The organic layer was washed with H_2O and brine, and then dried. After evaporation of the solvent, the oily product was purified by chromatography on silica gel. Elution with *n*-hexane–EtOAc (v/v, 2/1) afforded 14 g (52%) of **25** as a solid.

2-Acetyl-3-amino-3-phenylacrylonitrile (26) A solution of **25** (7.6 g, 35 mmol) in CH_2Cl_2 (30 ml) was added to a solution of 13% NH_3–MeOH (30 ml) at 0 °C. The mixture was stirred for 30 min, then was evaporated, and the residue was purified by chromatography on silica gel. Elution with CH_2Cl_2–EtOAc (v/v, 5/1) afforded 5.84 g (88.8%) of **26** as crystals, mp 157—159 °C (EtOAc–*n*-hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.45 (3H, s), 6.00 (1H, br s), 7.45—7.65 (5H, m), 10.90 (1H, br s). *Anal.* Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 71.09; H, 5.55; N, 15.07.

4-Chloro-2-phenyl-3-nicotinonitrile (28) A solution of $POCl_3$ (50.7 ml) in CH_2Cl_2 (150 ml) was added dropwise to a solution of DMF (46.5 ml) in CH_2Cl_2 (450 ml) at −5 °C. The mixture was allowed to warm to room temperature and stirred for 30 min. To the CH_2Cl_2 solution of Vilsmeier reagent, **26** (33.7 g, 181 mmol) was added in one portion at −10 °C, with further CH_2Cl_2 (150 ml). The red solution was gradually warmed to room temperature. After stirring for 3 h, the mixture was carefully neutralized by addition of aqueous Na_2CO_3. The CH_2Cl_2 layer was separated and the aqueous layer was extracted with CH_2Cl_2 (150 ml × 2). The extract was washed with H_2O and brine, and then dried. After removal of the solvent, the residue was dissolved in MeOH (600 ml) and this solution was allowed to stand overnight. The methanolic solution was concentrated *in vacuo* and the residue was partitioned between EtOAc and H_2O. The aqueous layer was extracted with EtOAc (150 ml × 3) and the extract was washed several times with H_2O and then brine. The solvent was dried and evaporated to afford several products, which were separated by chromatography on silica gel. Elution with CH_2Cl_2 afforded 25.4 g (65.3%) of **28**, mp 100—102 °C (EtOAc–*n*-hexane). ^{1}H-NMR ($CDCl_3$) δ: 7.46 (1H, d, J=5.4 Hz), 7.47—7.60 (3H, m), 7.85—7.95 (2H, m), 8.74 (1H, d, J=5.4 Hz). IR (Nujol): 2222, 1620, 1557, 1535 cm^{-1}. *Anal.* Calcd for $C_{12}H_7ClN_2$: C, 67.15; H, 3.29; Cl, 16.52; N. 13.05. Found: C, 67.26; H, 3.34; Cl, 16.44; N, 12.99.

4-Azido-2-phenyl-3-nicotinonitrile (29) A mixture of **28** (25.37 g, 118 mmol) and NaN_3 (11.9 g, 178 mmol) in DMF (142 ml) was heated at 75 °C for 15 min and concentrated *in vacuo*. The resulting crude crystals were collected, washed with H_2O, and taken up in EtOAc. The organic layer was washed with brine, dried and evaporated. The residue was purified by chromatography on silica gel. Elution with CH_2Cl_2–EtOAc gave 23.8 g (91%) of **29**, mp 123—125 °C (EtOH). ^{1}H-NMR ($CDCl_3$) δ: 7.15 (1H, d, J=5.6 Hz), 7.46—7.57 (3H, m), 7.82—7.95 (2H, m), 8.77 (1H, d, J=5.6 Hz). IR (Nujol): 2216, 2120, 1555 cm^{-1}. *Anal.* Calcd for $C_{12}H_7N_5$: C, 65.15; H, 3.19; N, 31.66. Found: C, 65.37; H, 3.40; N, 31.58.

4-Azido-2-phenyl-3-nicotinamide (30) A suspension of **29** (23.7 g, 107 mmol) in concentated H_2SO_4 (131 ml) was heated at 70 °C for 6 h and cooled to room temperature. The mixture was poured onto ice and neutralized with aqueous NaOH. The precipitate was collected, thoroughly washed with H_2O, and then dried *in vacuo* to afford 25.0 g (97.4%) of **35**, mp 156 °C (dec.) ($CHCl_3$–EtOH). ^{1}H-NMR (DMSO-d_6) δ: 7.42 (1H, d, J=5.6 Hz), 7.38—7.48 (3H, m), 7.62 (1H, br s), 7.65—7.76 (2H, m), 7.90 (1H, br s), 8.62 (1H, d, J=5.4 Hz). IR (Nujol): 3374, 3170, 2120, 1656, 1622, 1567 cm^{-1}. *Anal.* Calcd for $C_{12}H_9N_5O$: C, 60.25; H, 3.79; N, 29.27. Found: C, 60.37; H, 3.89; N, 29.19.

3-Amino-4-azido-2-phenylpyridine (31) Bromine (5.7 ml, 110 mmol) was added dropwise to a solution of 4 N NaOH (83 ml) and H_2O (58.5 ml) at 0 °C and the mixture was stirred for 10 min. Then a suspension of **30** (18.85 g, 78.8 mmol) in CH_2Cl_2 (140 ml) was added; the reaction was slightly exothermic. Stirring was continued for 3 h, then the organic layer was removed and the aqueous layer was washed twice with CH_2Cl_2. The aqueous layer was adjusted to pH 8 with 1 N HCl and extracted with CH_2Cl_2 (150 ml × 3). The CH_2Cl_2 solution was washed with brine, dried and then concentrated to afford 14.8 g (89%) of **31**, mp 119—121 °C (EtOAc–*n*-hexane). ^{1}H-NMR ($CDCl_3$) δ: 3.98 (2H, br s), 6.95 (1H, d, J=5.2 Hz), 7.35—7.54 (3H, m), 7.61—7.70 (2H, m), 8.11 (1H, d, J=5.2 Hz). IR (Nujol): 3418, 3296, 2108, 1576 cm^{-1}. SIMS *m/z*: 212 $(M+H)^+$. *Anal.* Calcd for $C_{11}H_9N_5$: C, 62.55; H, 4.29; N, 33.16. Found: C, 62.74; H, 4.43; N, 33.01.

3,4-Diamino-2-phenylpyridine (32) The reduction of **31** was carried out according to the procedure described for **10** to give **32** as a foam, which was used without purification in the next step. ^{1}H-NMR ($CDCl_3$) δ: 3.32 (2H, br s), 4.08 (2H, br s), 6.53 (1H, d, J=5.2 Hz), 7.30—7.50 (3H, m), 7.53—7.62 (2H, m), 7.93 (1H, d, J=5.2 Hz).

2-*n*-Butyl-4-phenyl-1*H*-imidazo[4,5-*c*]pyridine (33) The preparation of **33** was carried out according to the procedure described for **11**. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, J=7.2 Hz), 1.25—1.45 (2H, m), 1.68—1.82 (2H, m), 2.84 (2H, t, J=7.2 Hz), 7.30—7.46 (4H, m), 8.10—8.30 (2H, m), 8.40 (1H, d, J=5.6 Hz).

2-*n*-Butyl-4-phenyl-1-[[2′-(2-trityl-2*H*-tetrazol-5-yl)biphenyl-4-yl]-methyl]-1*H*-imidazo[4,5-*c*]pyridine (34) The preparation of **34** was carried out according to the procedure described for **12**. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.2 Hz), 1.35—1.50 (2H, m), 1.75—1.90 (2H, m), 2.82 (2H, t, J=7, 2 Hz), 5.23 (2H, s), 6.78 and 7.10 (2H × 2, ABq, J=8.2 Hz), 6.85—6.98 (4H, m), 7.15—7.60 (10H, m), 7.90—7.96 (1H, m), 8.33 (1H, d, J=5.4 Hz), 8.60—8.70 (2H, m).

2-*n*-Butyl-4-phenyl-1-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-imidazo[4,5-*c*]pyridine (35) The preparation of **35** was carried out according to the procedure for **1**. mp 238—240 °C (MeOH). ^{1}H-NMR (DMSO-d_6) δ: 0.88 (3H, t, J=7.2 Hz), 1.30—1.50 (2H, m), 1.62—1.80 (2H, m), 2.90 (2H, t, J=7.2 Hz), 5.58 (2H, s), 7.08 (4H, s), 7.40—7.72 (8H, m), 8.39 (1H, d, J=5.6 Hz), 8.70—8.80 (2H, m). *Anal.* Calcd for $C_{30}H_{27}N_7$: C, 74.20; H, 5.60; N, 20.19. Found: C, 73.93; H, 5.63; N, 20.06.

Angiotensin II Receptor Binding Assay A cDNA encoding human AT_1 angiotensin II receptor, donated by Dr. T. Inagami (Vanderbilt University, U.S.A.), was inserted into the mammalian expression vector pcDNA1 (Invitrogen). COS-7 cells were plated in 175-cm^2 flasks and grew to 80% confluency after 3 d. The cells were then transfected with 40 μg of DNA by using 150 μl of lipofectin reagent (GIBCO). Two or three days after transfection, binding assay was done as described previously.[12] In brief, cell suspensions (1.2×10^6 cell/ml), dispersed with 0.025% trypsin/1 mM EDTA, were incubated at 25 °C for 60 min in 0.2 ml of Hepes (20 ml) buffered Hanks' solution containing 1 mg/ml phenylmethylsulfonyl fluoride, 10 μg/ml aprotinin, 10 μg/ml leupeptin, 10 μg/ml pepstatin A, 250 μg/ml bacitracin, 10 μg/ml soybean trypsin inhibitor and 0.1 mM amastatin with 0.1 nM [^{125}I]AII (81.4 TBq/mmol, New England Nuclear) in the absence or presence of non-radioactive peptides or drugs. Each binding reaction was terminated by addition of 2.5 ml of ice-cold 50 mM Tris–HCl (pH 7.4), followed by rapid filtration through a GF/C glass fiber filter under reduced pressure. The filters were then quickly washed 4 more times with 2.5 ml of the Tris buffer, and the radioactivity retained on the filter was counted. Nonspecific binding, determined in the presence of 10^{-6} M non-radiolabeled AII, was 5—10% of the total binding. The K_i values were calculated from the equation $K_i = IC_{50}/(1+[L]/K_d)$, where IC_{50} = the concentration causing 50% inhibition of specific [^{125}I]AII binding, [L] = [^{125}I]AII concentration, and K_d = the dissociation constant for [^{125}I]AII (0.46 nM).

Evaluation of AII Antagonists in Conscious, SHRs Male SHRs (280—350 g) were anesthetized with pentobarbital sodium (60 mg/kg i.p.). An arterial catheter was surgically implanted. Briefly, a polyethylene catheter was placed into the femoral artery; this catheter was used for recording the arterial pressure of conscious, freely moving animals. The catheter was tunneled subcutaneously to the back of the head. After the rats had completely recovered from anesthesia (at least 2.5 h after surgery), the arterial catheter was connected to a pressure transducer-coupled polygraph for monitoring of the arterial pressure. After a 1-h stabilization period, rats were given the vehicle (saline, polyethylene glycol or 1% gum arabic) or a test compound by gavage, and the blood pressure was monitored for 4 h.

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