2-(Alkylamino)nicotinic Acid and Analogs. Potent Angiotensin II Antagonists[1]

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A series of pyridines and other six-membered ring heterocycles connected to a biphenylyltetrazole with a $-CH_2-NR'-$ link (1) were discovered to be potent angiotensin II antagonists. In the pyrimidine carboxylic acid series (W = CR, X = N, Y = CH, Z = COOH), compounds with an alkyl group (R′) on the exocyclic nitrogen were much more potent than compounds with an alkyl group (R) on the heterocyclic ring. The corresponding pyridine, pyridazine, pyrazine, and 1,2,4-triazine carboxylic acids also showed potent in vitro angiotensin II antagonism. The pyridine (W, X, Y = CH, Z = COOH, R′ = n-C_3H_7) demonstrated potent in vitro activity (pA_2 = 10.10, rabbit aorta, and K_i = 0.61 nM, receptor binding in rat liver) as well as exceptional oral antihypertensive activity and bioavailability. Any nonacidic replacement for the carboxylic acid was detrimental for activity.

The renin–angiotensin system (RAS) is known to play an important role in cardiovascular regulation. On the basis of the success of the angiotensin-converting enzyme inhibitors as antihypertensive drugs, there has been intense effort in the pharmaceutical industry to discover renin inhibitors and angiotensin II (A-II) antagonists as alternative means of inhibiting the RAS. The development of nonpeptide A-II antagonists was initiated by Takeda chemists, who reported on imidazoles such as **2a**, which possessed weak activity.[2] DuPont scientists subsequently discovered the importance of linking the imidazole to a biphenylyltetrazole moiety, leading to the discovery of the orally active DUP-753 (Losartan **2b**),[3] which is in clinical trials.

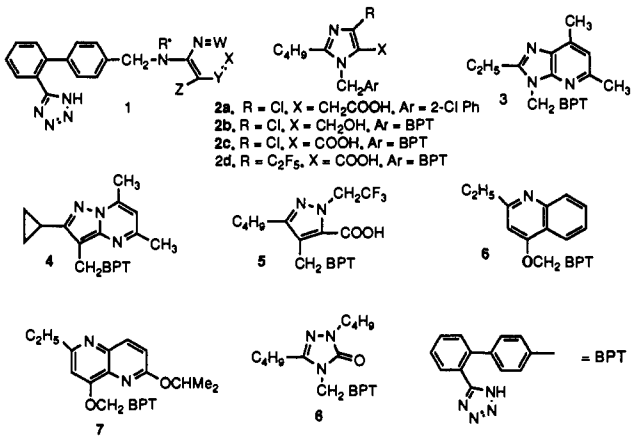
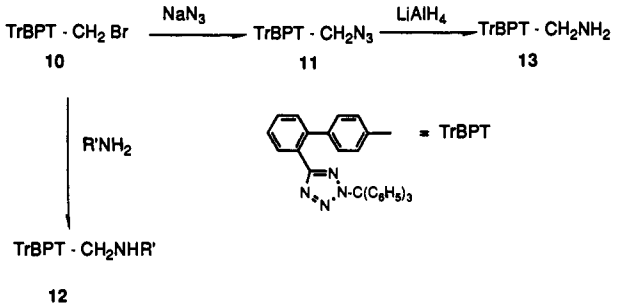


Figure 1.

Since then, there have been many other reports of A-II antagonists that contain an alkyl-substituted nitrogen heterocycle connected to a biphenylyltetrazole by a methylene or an ether link. Examples of these heterocycles include imidazo[4,5-b]pyridine (3),[4] pyrazolo[1,5-a]pyrimidine (4),[5] pyrazole (5),[6,7] quinoline (6),[8] 1,5-naphthyridine (7),[9] and triazolones (8).[10]

At the start of our work, only the imidazole-containing A-II antagonists **2a–d** were known. We chose to examine related compounds based on six membered ring heterocycles. From the published structures, it appeared that a target compound should incorporate a carboxylic acid, an alkyl group, and a tetrazole-substituted biphenyl moiety, each attached to the central heterocycle. What remained to be determined, however, was the exact placement of these groups on a six membered ring, and the optimum choice for the heterocycle itself.

Scheme I



Heterocycles that incorporated a number of these features, such as pyrimidines **9**[11] (Scheme II) and pyridines **29** (Scheme VI), were readily synthesized. Furthermore, they contained a reactive chlorine through which the biphenylyltetrazole group could be easily attached via a heteroatom linkage. A nitrogen was chosen for this purpose since an amine was sufficiently reactive to add to the activated heterocycles and the nitrogen would also provide a region for additional structure exploration.

Chemistry

The chloropyrimidines **9**[11] were directly coupled (see Scheme II) with amino derivatives of the biphenylyltetrazole (**12** and **13**). These were prepared from the known (bromomethyl)biphenylyltetrazole[12] (see Scheme I). The trityl-protected compounds (**14**) were deprotected under acidic conditions to give the esters, which were then hydrolyzed with base to the carboxylic acids **16**. Alcohols **17** were obtained by reduction of **14** with $LiAlH_4$ followed by detritylation with acid. When R = $CH_3OCH_2CH_2$, **9** could not be prepared from the corresponding hydroxyl compound without cleaving the ether. Instead the product

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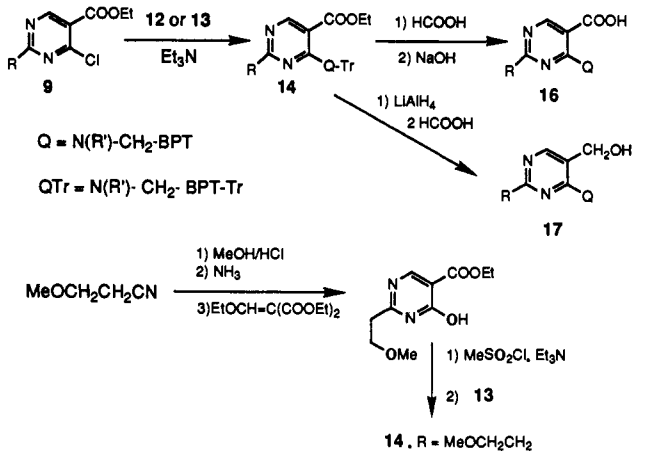
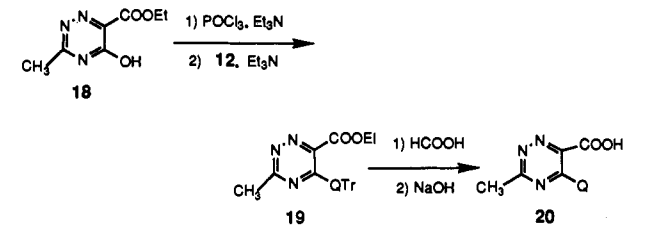
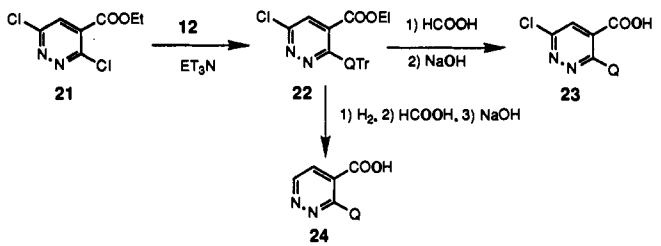
Scheme II



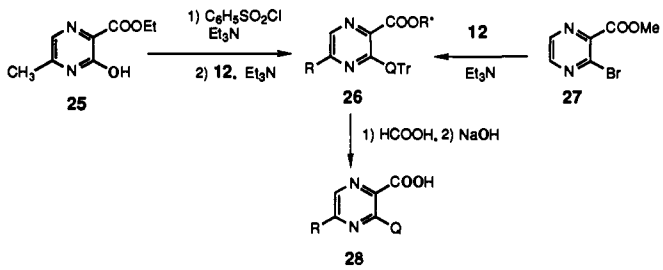
Scheme III



Scheme IV



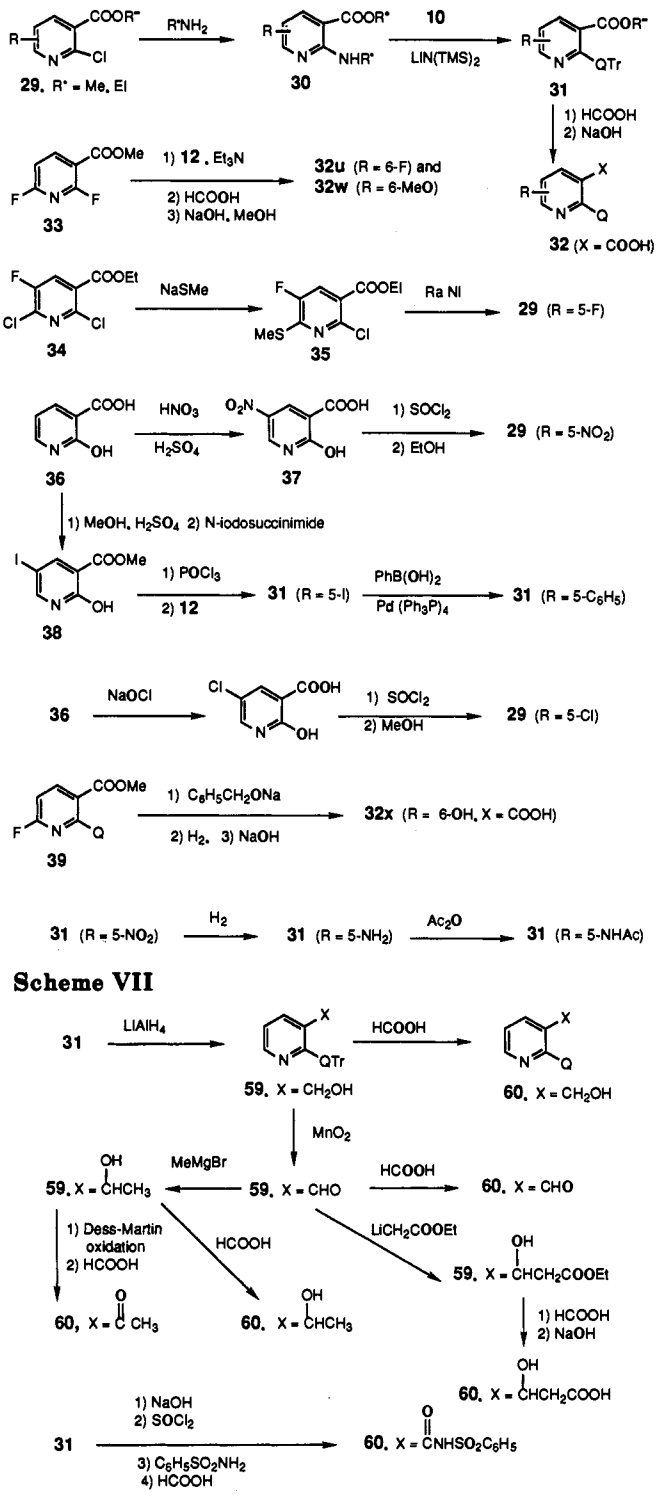
Scheme V



was made by way of the methanesulfonate intermediate (see Scheme II). Similarly, 1,2,4-triazines, pyrazines, and pyridazines were prepared from esters 18, 21, and 25, respectively, using halogen or benzenesulfonate leaving groups (see Schemes III–V).

The chloronicotinates 29 (R = H, Me, and Cl) did not react with the secondary amine 12. Therefore these pyridines were constructed in two steps (Scheme VI). Reaction of primary amines with 29 yielded 2-(alkylamino)-nicotinates 30, which were alkylated with bromide 10 to give the protected compounds 31. When R = 6-F, 5-F, or 5-I, the 2-chloro group in 29 could be directly displaced with the secondary amine 12. Ethyl 2,6-difluoronicotinate[14] reacted with 12 in the desired 2-position, based on the diagnostic splitting observed between the 6-F and 5-H in the ^{1}H NMR spectrum. The 5-fluoro compound was prepared from the known[15] compound 34, by displacement with methyl mercaptan in the 6-position (structure de-

Scheme VI



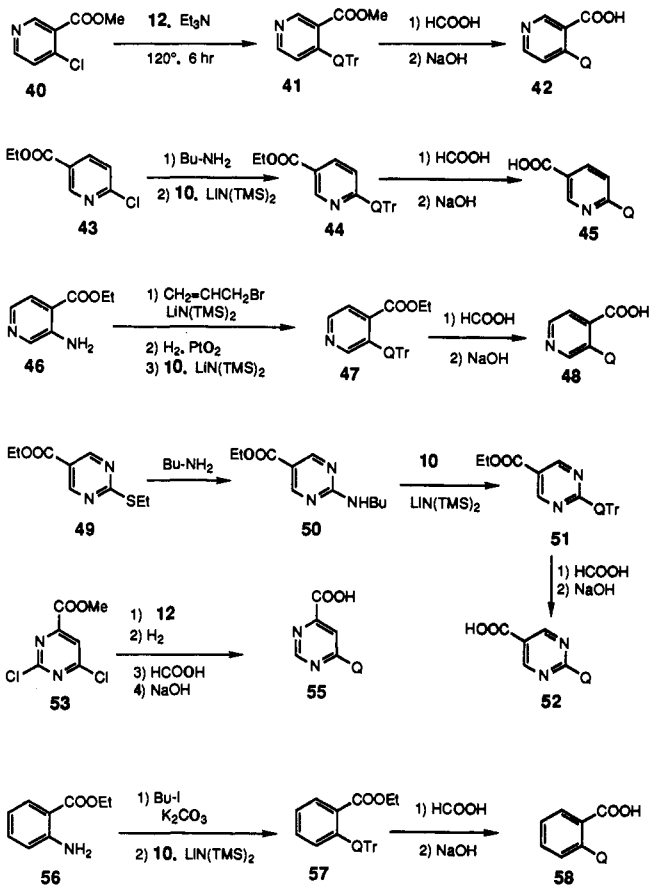
Scheme VII

termination by X-ray) and subsequent desulfurization of 35 with Raney nickel to give 29 (R = 5-F).

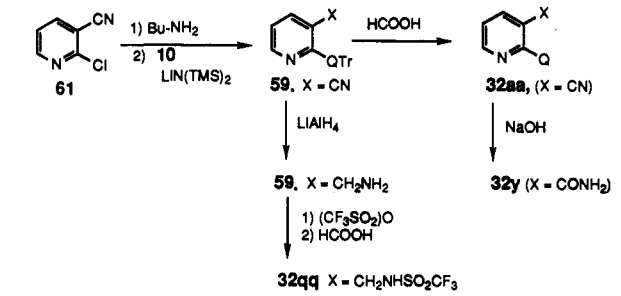
The other substituents (Cl, I, NO_2) at the 5-position of the nicotinic acid were introduced by way of electrophilic substitution on 36 (see scheme VI). The 5-phenyl analog was conveniently made by a palladium-catalyzed coupling reaction of the 5-iodo ester 31 with phenyl boronic acid. The 6-hydroxy compound was prepared from the 6-fluoro compound as shown.

The 5-carbethoxy group in 31 was converted to CH_2OH, CHO, CH(OH)Me, $CH(OH)CH_2COOH$, $COCH_3$, and $CONHSO_2C_6H_5$ groups as outlined in Scheme VII. The starting material for the synthesis of the 3-CN, $CONH_2$, and $CH_2NHSO_2CF_3$ analogs was 2-chloronicotinitrile

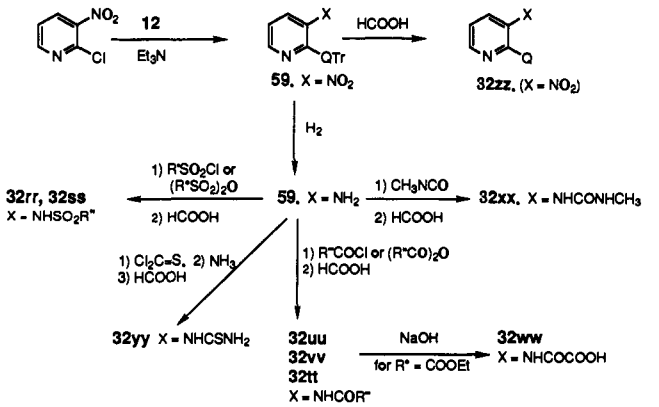
Scheme VIII



Scheme IX

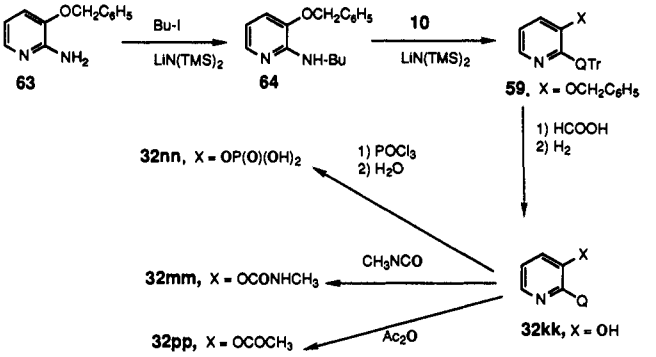


Scheme X

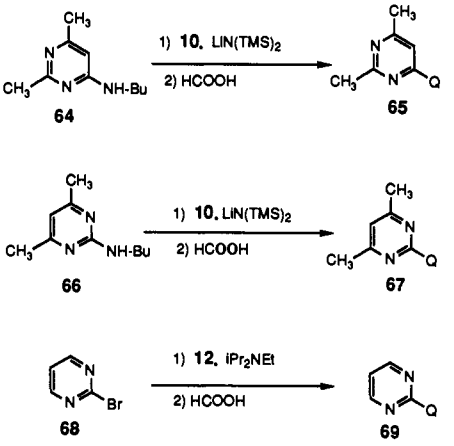


(Scheme IX). 3-Nitro-2-chloropyridine reacted with 12 to yield the nitro compound 59, which was converted into a wide variety of 3 nitrogen-substituted nicotinic acid analogs as shown in Scheme X. Commercially available 2-amino-3-(benzyloxy)pyridine (63) was transformed into several 3-oxygen-substituted analogs as shown in Scheme XI.

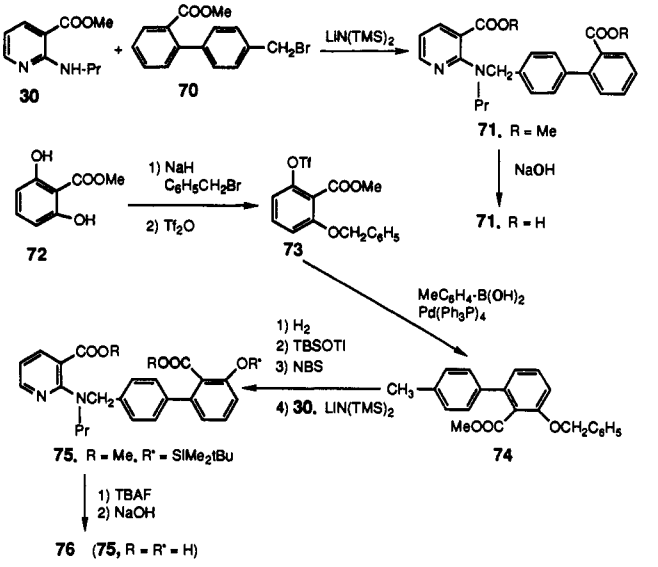
Scheme XI



Scheme XII

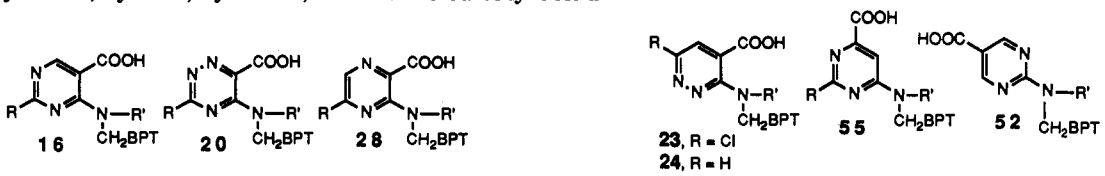


Scheme XIII



All of the above compounds possessed a common alkylamino linking group which was flanked on one side by a carboxyl or other polar group, and on the other side by a ring nitrogen. To study the effect of varying the position of the ring nitrogen and carboxylic acid relative to the linking group, other pyridines and pyrimidines were synthesized (Scheme VIII). The methods used were as follows: (1) direct secondary amine 12 displacement of a halo heterocycle (i.e. 40 and 53); (2) sequential displacement and alkylation (i.e. 43 and 49); and (3) double alkylation of a heterocyclic primary amine (46 and 56). The simple methyl and unsubstituted pyrimidine analogs were synthesized from the known starting materials 64, 66, and 68 (Scheme XII).

Table I. Pyrmidine, Pyrazine, Pyridazine, and Triazine Carboxylic Acids



no.	R	R′	pA_2[a]	mp[b] (°C)	formula[c]
16a	H	H	5.61 (0.08) 2	a	$C_{18}H_{15}N_7O_2{\cdot}0.65C_2H_5OH$
16b	CH_3	H	7.50 (0.11) 2	211–212	$C_{20}H_{17}N_7O_2{\cdot}HCl{\cdot}H_2O$
16c	C_2H_5	H	8.30 (0.04) 2	200–202	$C_{21}H_{19}N_7O_2{\cdot}HCl{\cdot}0.5H_2O$
16d	C_3H_7	H	8.27 (0.37) 2	223–225	$C_{22}H_{21}N_7O_2{\cdot}HCl$
16e	C_4H_9	H	7.91 (0.23) F	193–195	$C_{23}H_{23}N_7O_2{\cdot}HCl{\cdot}0.33H_2O$
16f	C_5H_{11}	H	7.23 (0.07) 2	166–168	$C_{24}H_{25}N_7O_2{\cdot}HCl{\cdot}H_2O$
16g	$CH_3OCH_2CH_2$	H	6.81 (0.01) 2	235	$C_{22}H_{21}N_7O_3{\cdot}0.5H_2O$
16h	C_4H_9	CH_3	7.15 (0.02) 2	165–169	$C_{24}H_{25}N_7O_2{\cdot}HCl{\cdot}H_2O$
16i	CH_3	C_2H_5	7.96 (0.02) 2	a	$C_{22}H_{21}N_7O_2{\cdot}0.70H_2O$
16j	CH_3	C_3H_7	9.60 (0.19) F	a	$C_{23}H_{23}N_7O_2{\cdot}0.75H_2O$
16k	CH_3	C_4H_9	8.81 (0.16) F[g]	155–158	$C_{24}H_{24}N_7O_2{\cdot}HCl{\cdot}0.5H_2O$
16l	CH_3	C_5H_{11}	8.73 (0.05) 2	a	$C_{25}H_{27}N_7O_2{\cdot}0.75H_2O$[d]
16m	CH_3	$CH_2CH{=}CH_2$	8.32 (0.14) F	a	$C_{23}H_{21}N_7O_2{\cdot}0.5HCl$[d]
16n	CH_3	CH_2CHMe_2	7.50 (0.04) 2	a	$C_{24}H_{25}N_7O_2{\cdot}0.5HCl$[d]
16o	CH_3	$(CH_2)_2CHMe_2$	8.85 (0.03) 2	a	$C_{25}H_{27}N_7O_2{\cdot}0.5HCl$
16p	CH_3	$CH_2CH_2OCH_3$	8.50 (0.01) 2	a	$C_{23}H_{23}N_7O_3{\cdot}0.75H_2O$
16q	H	C_3H_7	9.68 (0.09(F	a	$C_{22}H_{21}N_7O_2{\cdot}0.35H_2O$
16r	H	C_4H_9	9.57 (0.16) F	a	$C_{23}H_{23}N_7O_2{\cdot}HCl$[e]
16s	C_3H_7	C_3H_7	8.52 (0.04) 2	a	$C_{25}H_{27}N_7O_2{\cdot}0.75H_2O$
16t	CF_3	C_3H_7	8.79 (0.09) 2	a	$C_{23}H_{20}F_3N_7O_2{\cdot}0.1H_2O$
16u	CH_3S	C_4H_9	8.38 (0.11) 2	a	$C_{24}H_{25}N_7O_2S{\cdot}HCl{\cdot}0.5H_2O$
55	H	C_4H_9	7.95 (0.06) 2	a	$C_{23}H_{23}N_7O_7{\cdot}0.25H_2O$
52		C_4H_9	8.48 (0.04) 2	a	$C_{23}H_{23}N_7O_2{\cdot}0.25H_2O{\cdot}0.1i\text{-PrOH}$
20	CH_3	C_3H_7	8.00 (0.07) F	a	$C_{22}H_{22}N_8O$[f]
28a	CH_3	C_3H_7	8.90 (0.03) 3	102–104	$C_{23}H_{23}N_7O_2{\cdot}Et_2O$
28b	H	C_4H_9	9.70 (0.10) 6	a	$C_{23}H_{23}N_7O_2$
23a	Cl	C_3H_7	8.31 (0.08) 2	a	$C_{22}H_{20}ClN_7O_2{\cdot}0.25i\text{-PrOH}$
23b	Cl	C_4H_9	9.04 (0.12) 2	a	$C_{23}H_{22}ClN_7O_2{\cdot}0.25i\text{-PrOH}$
24a	H	C_3H_7	9.69 (0.20) 6	a	$C_{22}H_{21}N_7O_2{\cdot}0.25i\text{-PrOH}$
24b	H	C_4H_9	10.25 (0.15) 4	a	$C_{23}H_{25}N_7O_2{\cdot}0.5H_2O$

[a] pA_2 in rabbit aorta (standard error), no. of determinations for estimated pA_2, or F for full pA_2. Slope for full pA_2 is between 0.95 and 1.15 unless otherwise noted. See Experimental Section. [b] "a" denotes amorphous or no attempt was made to crystallize the compound. [c] Analysis for C, H, and N are within ±0.4% of theory. [d] Nitrogen low by 0.4 to 1.0%. [e] C: calcd, 59.29; found, 60.07. [f] H: calcd, 5.15; found, 5.68. [g] Slope = 1.21.

The benzoic and salicylic acid analogs of the phenyltetrazole were synthesized as outlined in Scheme XIII. Starting material **70**[12] was used in place of **10** to prepare the carboxylic acid **71**. The salicylic acid was synthesized by a palladium coupling of triflate **73** with tolyl boronic acid to give biphenyl **74** which was ultimately converted to the desired compound **76**.

Biology

Antagonism of Angiotensin II in the Rabbit Aorta. The compounds were evaluated for their potency in antagonizing the ability of angiotensin II to contract the rabbit aorta. Potencies were calculated as pA_2 values, the definition of which is as follows. If at drug concentration of 10^{-x} molar in the bath, one must double the concentration of angiotensin II to get the same effect on the rabbit aorta that one gets without the drug, then the pA_2 is x. The higher the pA_2 value, the more potent the drug. The standard error in the pA_2 determination varies, but we would consider a pA_2 difference of 0.25 between two compounds to be meaningful. See the Experimental Section for the difference between a full and estimated pA_2, and for the definition of the slope.

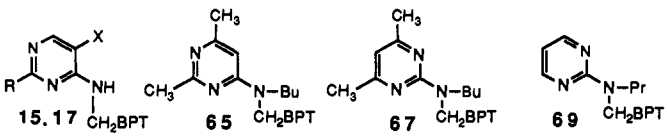
Our first series of compounds were the CH_2NH linked 2-alkyl pyrimidine carboxylic acids (Table I, compounds **16a–g**). The 2-ethyl and 2-propyl compounds had pA_2 values of 8.27 and 8.30, respectively, in the rabbit aorta, and thus were comparable in vitro to DUP-753. Shorter or longer alkyl groups weakened activity. The corresponding esters and alcohols (Table II) were roughly 3-fold weaker.

Conversion of the secondary amine in the linking group to a tertiary amine improved in vitro potency. Highly potent A-II antagonists were achieved with the *n*-propyl **16q** and *n*-butyl **16r** derivatives. The optimal substituent in the 2-position was hydrogen. Pyrimidine isomers (**52** and **55**) were much less potent.

The methyltriazine **20** was less active than the corresponding pyrimidine **16j**, while the pyrazine **28b** and pyridazine **24b** were equal or slightly more active than the corresponding pyrimidine **16k**. A chlorine on the pyridazine ring (**23**) reduced potency.

Removing one of the nitrogens in the pyrimidine ring resulted in the pyridine series which proved to be 5-fold more potent (compare **32c**, Table III to **16q**, Table I). The optimal substituent on the exocyclic nitrogen was either *n*-propyl or *n*-butyl. Any substitution on the pyridine ring (Table IV) reduced the activity; the most detrimental being 6-MeO or 6-OH; the least detrimental being 4-CH_3, 5- or 6-F, and 5-Cl. The 5-position could tolerate a degree of bulk, e.g. phenyl, but polar groups, e.g. AcNH or NH_2 were not accommodated. Compound **32f** with a pA_2 of 10.33 and **32c** (A-81988) with a pA_2 of 10.10 are among the best angiotensin II antagonists described to date (see Table VII). A-81988, **16q**, and **16r** showed competitive antagonism (slopes = 1.06–1.09) whereas L158809 (**3**, slope = 1.37), DUP-532 (**2d**, slope = 1.81), EXP-3174 (**2c**, slope =

Table II. SAR of 2-Alkylpyrimidines—Noncarboxylic Acids



no.	R	X	pA_2[a]	mp[b] (°C)	formula[c]
15a	H	COOEt	6.24 (0.08) 2	a	$C_{21}H_{19}N_7O_2$
15b	CH_3	COOEt	7.13 (0.07) 2	121–123	$C_{22}H_{21}N_7O_2$
15c	C_2H_5	COOEt	7.78 (0.05) 4	114–116	$C_{23}H_{23}N_7O_2$
15d	C_3H_7	COOEt	7.91 (0.02) 2	132–133	$C_{24}H_{25}N_7O_2$
15e	C_4H_9	COOEt	7.37 (0.02) 2	145–146	$C_{25}H_{27}N_7O_2$
15f	C_5H_{11}	COOEt	6.37 (0.32) 2	131–133	$C_{26}H_{29}N_7O_2$
15g	$CH_3OCH_2CH_2$	COOEt	7.10 (0.03) 2	122–124	$C_{24}H_{25}N_7O_3$[d]
17b	CH_3	CH_2OH	7.12 (0.06) 2	199–201	$C_{20}H_{19}N_7O\cdot HCl$
17c	C_2H_5	CH_2OH	7.96 (0.02) 2	217–219	$C_{21}H_{21}N_7O\cdot HCl$
17d	C_3H_7	CH_2OH	7.60 (0.44) F	214–216	$C_{22}H_{23}N_7O\cdot HCl$
17e	C_4H_9	CH_2OH	7.53 (0.21) F	152–159	$C_{23}H_{25}N_7O\cdot HCl$
17g	$CH_3OCH_2CH_2$	CH_2OH	6.41 (0.11) 2	218–220	$C_{22}H_{23}N_7O_2\cdot HCl$
65			7.90 (0.06) 3	a	$C_{24}H_{27}N_7\cdot 1.5H_2O$[d]
67			7.65 (0.10) F	148–150	$C_{24}H_{27}N_7$
69			8.08 (0.02) 2	a	$C_{21}H_{21}N_7$

[a–d] See Table I.

Table III. 2-(Alkylamino)nicotinic Acids—SAR of the N Substituent

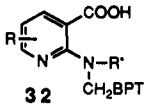
no.	R′	pA_2[a]	mp[b] (°C)	formula[c]
32a	H	<6.0	a	$C_{20}H_{16}N_6O_2$[d]
32b	C_2H_5	8.77 (0.07) 2	188–191	$C_{22}H_{20}N_6O_2$
32c	C_3H_7	10.10 (0.08) F[f]	202–203	$C_{23}H_{22}N_6O_2$
32d	$CH_2CH{=}CH_2$	9.00 (0.07) 3	a	$C_{23}H_{20}N_6O_2\cdot 0.33H_2O$
32e	CH_2-c-C_3H_5	8.48 (0.01) 2	a	$C_{24}H_{22}N_6O_2$
32f	C_4H_9	10.33 (0.03) 2	203–205	$C_{24}H_{24}N_6O_2$
32g	$CH_2CH_2CHMe_2$	8.96 (0.03) 2	212–213	$C_{25}H_{23}N_6O_2$[e]
32h	C_5H_{11}	9.07 (0.06) 2	92–93	$C_{25}H_{26}N_6O_2$[e]

[a–d] See Table I. [e] High-resolution MS within 0.004 of theory. [f] Combined calculation from 41 tissues.

1.39), and the ICI compound **7** (slope = 1.28) are noncompetitive antagonists.[35] The exocyclic alkylamino-linked heterocycles represented by A-81988, **16q**, **20**, **28b**, and **24b** represent a distinct class of angiotensin II antagonists.

Changing the 3-COOH in A-81988, or its *N*-butyl analog **32f**, to other functional groups significantly reduced potency (Table V). The methyl ester **32z** was less active by a factor of 1000, and the alcohol **32bb** by a factor of 400. In the corresponding pyrimidines also containing an exocyclic *n*-propyl or *n*-butyl group, we also noted a similar loss in potency when the acid was converted to the ester and alcohol (data not shown). This contrasts with the results seen in the pyrimidine series containing a secondary exocyclic nitrogen (see Table II), where the esters **15c–d** and alcohols **17c–d** were only 3-fold weaker than the acids **16c–d**. Similarly the alcohol DUP-753 (**2b**) is only 20-fold weaker than the corresponding acid (EXP-3174, **2c**) (Table VIII). Other acidic groups [$CH(OH)CH_2COOH$, $CONHSO_2C_6H_5$, $OPO(OH)_2$, and $NHSO_2CF_3$, compounds **32gg**, **qq**, **nn**, and **rr** of Table VI] imparted good activity, albeit not as potent as A-81988. Of the groups that are neutral at pH = 7.4, only the primary amide **32g** and the aldehyde **32cc** had pA_2 values greater than 8.0. Thus, a

Table IV. 2-(Alkylamino)nicotinic Acids—SAR of Substituents on the Pyridine Ring



no.	R	R′	pA_2[a]	formula
32c	H	C_3H_7	10.10 (0.08) F[f]	$C_{23}H_{22}N_6O_2$[d]
32j	4-CH_3	C_3H_7	9.64 (0.02) 2	$C_{24}H_{24}N_6O_2$[d]
32k	5-CH_3	C_3H_7	8.80 (0.09) 2	$C_{24}H_{24}N_6O_2$[d]
32l	5-Cl	C_3H_7	9.07 (0.04) 2	$C_{23}H_{21}ClN_6O_2$
32m	5-F	C_3H_7	9.04 (0.02) 2	$C_{23}H_{21}FN_6O_2\cdot 0.6CF_3COOH$
32n	5-I	C_4H_9	8.38 (0.15) F	$C_{24}H_{23}IN_6O_2\cdot 0.6CF_3COOH$
32p	5-C_6H_5	C_3H_7	8.91 (0.20) 2	$C_{29}H_{26}N_6O_2\cdot 1.5H_2O$[e]
32q	5-NO_2	C_3H_7	8.33 (0.03) 2	$C_{23}H_{21}N_7O_4\cdot 1.5H_2O$
32r	5-NH_2	C_3H_7	7.60 (0.03) 2	$C_{23}H_{23}N_7O_2$[d]
32s	5-$NHCOCH_3$	C_3H_7	7.90 (0.02) 2	$C_{25}H_{25}N_7O_3\cdot 1.33H_2O$
32t	6-CH_3	C_4H_9	8.15 (0.07) 2	$C_{25}H_{26}N_6O_2$
32u	6-F	C_3H_7	9.63 (0.30) 2	$C_{23}H_{21}FN_6O_2\cdot 0.75CF_3COOH$
32w	6-CH_3O	C_3H_7	7.78 (0.02) 3	$C_{24}H_{24}N_6O_3\cdot 0.9CF_3COOH$
32x	6-OH	C_3H_7	<6.0	$C_{23}H_{22}N_6O_3\cdot 1.5H_2O$

[a,c,d] See Table I. [e] H: calcd, 5.65; found, 5.07. [f] See Table III.

second acidic group on the heterocycle is needed for high potency in our series, but one not required in compound **3**, **6**, and **7**, (see Figure 1) all of which have similar potency to A-81988.

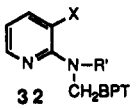
As observed with the pyrimidines, moving the ring nitrogen or the carboxylic acid relative to the exocyclic amine decreased in vitro potency (Table VI). Eliminating the ring nitrogen yielded the anthranilic acid **58**, which was a very weak A-II antagonist.

Replacing the tetrazole in A-81988 with a carboxylic acid yielded compound **71** with a pA_2 = 7.49. Since the tetrazole is more acidic than the carboxylic acid, the salicylic acid analog **76** was prepared on the basis of the fact that salicylic acid is 15 times more acidic than benzoic acid.[32] However the salicylate **76** did not significantly improve the potency (pA_2 = 7.79), suggesting that the increased potency of the tetrazole relative to the carboxylic acid was not due solely to its greater acidity. Our results differ from the DUP-753 series where the carboxylic acid is only 20-fold less potent than the tetrazole, whereas in our compounds, the difference is a factor of 400.

Radioligand Binding. Our best compounds, A-81988 (**32c**) and the pyrimidine analog **16r**, exhibited radioligand binding to angiotensin II (type I) receptors in rat liver in the nanomolar range, similar to that of the Merck compound, L-158809. A-81988 and three other compounds (**16e**, **16d**, and **16k**) were tested for binding to the angiotensin II (type 2) receptor in the bovine cerebellum and showed no binding at a 30 μM concentration. In general the pA_2 values correlate well with the binding data (see Table VIII).

In Vivo Antihypertensive Activity. Oral antihypertensive activity was assessed in various rat models (Table VIII). The pyrimidine ester **15c** demonstrated oral activity at 10 mg/kg whereas the corresponding pyrimidine acid **16c**, while more potent in vitro, showed no activity in the renal artery ligated hypertensive rate (RALHR) model. Compound **32c** (A-81988) demonstrated oral activity for up to 24 hr in the RALHR model at 0.03 mg/kg, in the furosemide treated spontaneously hypertensive rat (FTSHR) model at 0.1 mg/kg, and in nontreated SHR

Table V. Pyridines—SAR of Substitution in the 3-Position

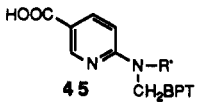


32

no.	X	R'	pA2[a]	mp[b] (°C)	formula[c]
32c	COOH	C_3H_7	10.10 (0.08) F[f]	202–203	$C_{23}H_{22}N_6O_2$
32f	COOH	C_4H_9	10.33 (0.03) 2	203–205	$C_{24}H_{24}N_6O_2$
32y	$CONH_2$	C_4H_9	8.58 (0.08) 2	194–197	$C_{24}H_{23}N_7O$[d]
32z	$COOCH_3$	C_3H_7	7.08 (0.15) 2	138–193	$C_{24}H_{24}N_6O_2$
32aa	CN	C_4H_9	7.68 (0.18) 2	173–174	$C_{24}H_{23}N_7 \cdot 0.5H_2O$
32bb	CH_2OH	C_3H_7	7.48 (0.01) 2	188–189	$C_{23}H_{24}N_6O \cdot 0.66H_2O$[d]
32cc	CHO	C_3H_7	8.56 (0.06) 2	a	$C_{23}H_{22}N_6O$[d]
32dd	$CH(OH)CH_3$	C_3H_7	7.26 (0.05) 2	83–85	$C_{24}H_{26}N_6O \cdot 0.5H_2O$
32ee	$COCH_3$	C_3H_7	7.00 (0.05) 2	a	$C_{24}H_{24}N_6O$[e]
32ff	$CH(OH)CH_2COOEt$	C_3H_7	7.88 (0.06) 2	a	$C_{27}H_{30}N_6O_3$[d]
32gg	$CH(OH)CH_2COOH$	C_3H_7	8.84 (0.01) 2	a	$C_{25}H_{26}N_6O_3 \cdot 0.5H_2O$
32hh	$CONHSO_2C_6H_5$	C_3H_7	8.65 (0.02) 2	a	$C_{29}H_{27}N_7O_3S$[d]
32jj	CH_3	C_4H_9	6.86 (0.02) 2	a	$C_{24}H_{26}N_6$[d]
32kk	OH	C_4H_9	7.53 (0.03) 2	a	$C_{23}H_{24}N_6O$[d]
32mm	$OCONHCH_3$	C_4H_9	7.34 (0.01) 2	a	$C_{25}H_{27}N_7O_2 \cdot 0.2CHCl_3$[d]
32nn	$OPO(OH)_2$	C_4H_9	8.44 (0.10) 2	a	$C_{23}H_{25}N_6O_4P$[e]
32pp	$OCOCH_3$	C_4H_9	7.65 (0.12) 2	a	$C_{25}H_{26}N_6O_2$
32qq	$CH_2NHSO_2CF_3$	C_4H_9	7.86 (0.07) 2	95–98	$C_{25}H_{26}F_3N_7O_2S$[d]
32rr	$NHSO_2CF_3$	C_3H_7	9.27 (0.21) 2	214–216	$C_{23}H_{22}F_3N_7O_2S$
32ss	$NHSO_2CH_3$	C_3H_7	7.98 (0.04) 2	137–140	$C_{23}H_{25}N_7O_2S \cdot 0.5H_2O$[d]
32tt	$NHCOCH_3$	C_3H_7	6.40 (0.06) 2	170–171	$C_{24}H_{25}N_7O$[d]
32uu	$NHCOCF_3$	C_3H_7	6.89 (0.04) 2	79–80	$C_{24}H_{22}F_3N_7O \cdot 0.25H_2O$
32vv	NHCOCOOEt	C_3H_7	7.68 (0.11) 2	a	$C_{29}H_{27}N_7O_3$[e]
32ww	NHCOCOOH	C_3H_7	7.65 (0.12) 2	a	$C_{24}H_{23}N_7O_3$[e]
32xx	$NHCONHCH_3$	C_3H_7	7.76 (0.04) 2	194–195	$C_{24}H_{26}N_8O \cdot 0.5H_2O$
32yy	$NHCSNH_2$	C_3H_7	7.34 (0.30) 2	a	$C_{23}H_{24}N_8S \cdot 0.5H_2O$[d]
32zz	NO_2	C_3H_7	7.92 (0.06) 4	176–178	$C_{22}H_{21}N_7O_2$

[a–d] See Table I. [e] High-resolution MS within 0.004 of theory. [f] See Table III.

Table VI. Pyridine and Benzene Carboxylic Acids—SAR of Positional Isomers



45

42, 48, 58

no.	A	B	R'	pA2[a]	formula[c]
45			C_4H_9	8.12 (0.06) 2	$C_{24}H_{24}N_6O_2$[d]
42	N	CH	C_3H_7	7.23 (0.01) 2	$C_{23}H_{22}N_6O_2 \cdot 0.2H_2O$
48	CH	N	C_3H_7	8.45 (0.03) 2	$C_{23}H_{22}N_6O_2 \cdot 0.25H_2O$
58	CH	CH	C_4H_9	6.91 (0.06) 2	$C_{25}H_{25}N_5O_2 \cdot 0.25H_2O$

[a,c,d] See Table I.

Table VII. Comparison of A-81988 to Literature Standards

compd	pA2[a]	slope[b]
A-818988 (**32c**)	10.10 (0.08) F[e]	1.07 (0.03)[e]
DUP 753 (**2b**)	8.43 (0.20) F	1.01 (0.07)
L 158809 (**3**)	9.63 (0.07) F	1.37 (0.06)
	10.6	if slope is forced to unity[c]
DUP 532 (**2d**)	8.80 (0.14) F	1.81 (0.20)
EXP 3174 (**2c**)	9.71 (0.15) F	1.39 (0.19)
	11.0	if slope is forced to unity[c]
IC compd (**7**)	9.12 (0.27) F	1.28 (0.21)
	10.0	if slope is forced to unity[c]

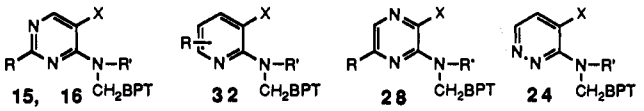
[a] See Table I. [b] Standard error in parnetheses. [c] This is calculated the same way as an estimated pA_2. See Experimental Section. [e] See table III, footnote *f*.

at 3.0 mg/kg. No reduction in blood pressure was observed in normotensive rats at 3 mg/kg, po. The alcohol **32bb**, the aldehyde **32cc**, and the ester **32z**, possible prodrugs of A-81988, were much less active. The *n*-butyl analog (**32f**) was slightly less active, while the pyrimidine **16r** was 30-fold less active than A-81988 when given orally. Substitution on the pyridine ring with 4-Me, 5-F, or 6-F yielded compounds that were significantly less potent in reducing blood pressure in FTSHR when administered orally. The trifluoromethane sulfonamide **32rr**, whose in vitro potency approached that of A-81988, was inactive in the RALHR at a 10-fold greater dose than that required to observe significant effects with A-81988. Compared to literature compounds, A-81988 was much more potent in vivo than DUP-753 (**2b**), and somewhat more potent than L-158809 (**3**). Pyridazine **24a** and pyrazines **28a** and **28b**, while potent in vitro, were significantly weaker than A-81988 when administered orally.

Pharmacokinetics. The exceptional oral antihypertensive activity of A-81988 (**32c**) as compared to the pyrimidine analog **16r** led us to initiate pharmacokinetic studies of the two compounds. A pharmokinetic profile of L-158809 (**3**) was also determined so a comparison to a literature compound could be made.

The pharmacokinetic parameters for the A-II antagonists in normal male Sprague–Dawley rats are provided in Table IX. The pyrimidine A-II antagonist **16r** was characterized by a low volume of distribution (V_1 = 0.08 L/kg, V_β = 0.42 L/kg) and a low plasma clearance [CLp = 0.85 ± 0.12 mL/min (mean ± SEM)] with a terminal elimination half-life of 1.5 h. Peak plasma concentrations (C_{max}) ranged from 0.51 to 1.5 mcg/mL following 3.87–23.4 mg/kg single oral doses and calculated bioavailability values were 5–10%. The pyridine analogue, A-81988, provided a substantial improvement in the plasma elimination half-life (6–9 h following IV bolus administration) coupled with a 2–3-fold decrease in the apparent volume of distribution (V_1 = 0.04 L/kg, V_β = 0.12–0.17 L/kg). The plasma clearance values averaged 0.07 ± 0.01 mL/min over the iv dose range of 0.3–3 mg/kg. A-81988 was rapidly absorbed after oral dosing with peak plasma concentrations recorded in the first 1–2 h. Plasma concentrations increased with increasing dose, although the increase was not proportional to the dose. Bioavailability values in

Table VIII. Radioligand Binding and in Vitro, and in Vivo Data for Selected Compounds



no.	R	R′	X	pA_2[a]	K_i (nM)[b]	RALHR[c]	FT SHR[d]
15c	C_2H_5	H	COOEt	7.78	20.6 (5.54–77.0) 3	30, 32(±5)%, 2 10, 14(±8)%, 2	
16c	C_2H_5	H	COOH	8.30	68.1 (31.9–145) 3	3 (iv) inact	
16e	C_4H_9	H	COOH	7.91		3 (iv) inact	
16j	CH_3	C_3H_7	COOH	9.60	2.78 (1.66–4.64) 3	30, 18(±9)%, 2 10, 15(±2)%, 2	
16k	CH_3	C_4H_9	COOH	8.81	15.3 (7.01–33.6) 3	30, 11(±10)%, 2	
16r	H	C_4H_9	COOH	9.57	1.77 (0.59–5.36) 3	10, 41(±6)%, 6 3, 18(±8)%, 4 1, 10(±4)%, 4	
32c	H	C_3H_7	COOH	10.10	0.61 (0.49–0.84) 3	1.0, 40(±4)%, 4 0.3, 36(±4)%, 7 0.01, 22(±6)%, 6 0.03, 10(±3)%, 7	1.0, 32(±1)%, 46(±2)%, 2 0.1, 23(±4)%, 36(±5)%, 6
32f	H	C_4H_9	COOH	10.33		0.3, 45(±7)%, 2 0.1, 16(±12)%, 2	0.3, 14(±3)%, 40(±4)%, 4 0.1, 5(±3)%, 22(±1)%, 4
32d	H	$CH_2CH{=}CH_2$	COOH	9.00			1.0, 13(±3)%, 31(±6)%, 4
32j	$4CH_3$	C_3H_7	COOH	9.64			1.0, 10(±3)%, 15(±3)%, 3
32m	5-F	C_3H_7	COOH	9.04			1.0, 6(±4)%, 22(±4)%, 2
32u	6-F	C_3H_7	COOH	9.63			1.0, 15(±1)%, 36(±7)%, 2
32z	H	C_3H_7	COOMe	7.08			1.0, inact
32bb	H	C_3H_7	CH_2OH	7.48		0.3, inact	
32cc	H	C_3H_7	CHO	8.56		0.3, 15(±2)%, 2	
32rr	H	C_3H_7	$NHSO_2CF_3$	9.27		0.3, 6(±0)%, 2	
24a		C_3H_7	COOH	9.69			1.0, 3(±0)%, 18(±5)%, 2
28a	CH_3	C_3H_7	COOH	8.90			1.0, 2(±3)%, 18(±6)%, 2
28b	H	C_4H_9	COOH	9.70			1.0, 7(±1)%, 21(±6)%, 2
DUP-753 (**2**)				8.43	14.6 (9.53–22.4) 8	10, 27(±2)%, 7 3, inact	10, 21(±2)%, 34(±5)%, 4
L-158809 (**3**)				9.63 nc	0.45 (0.14–1.45) 3	3.0, 32(±9)%, 4 0.3, 25(±3)%, 4 0.1, 15(±2)%, 4 0.03, 8(±1)%, 4	1.0, 32(±5)%, 30(±8)%, 2
EXP-3174 (**2c**)				9.71 nc		10, 40(±8)%, 2	

[a] For standard errors and slope, see other tables. [b] K_i (95% confidence limits), *n*. [c] Renal artery hypertensive rat model (dose in mg/kg), % decrease in bp at 4 h, (±SEM), number of rats. [d] Furosemide-treated spontaneous hypertensive rat model (dose in mg/kg), % decrease in bp at 4 h, (±SEM), % decrease in bp at 24 hr, (±SEM), number of rats.

Table IX. Pharmacokinetic Evaluation of Selected Angiotensin II Antagonists in Male Sprague–Dawley-Derived Rat

	intravenous dose						oral dose					
compd	dose (mg/kg)	$t_{1/2}\beta$[a] (h)	V_1[b] (L/kg)	V_β[c] (L/kg)	CL_p[d] (mL/min)	*n*	$t_{1/2}\beta$[a] (h)	C_{max}[e] (μg/mL)	T_{max}[f] (h)	$AUC_{0-\infty}$[g] (μg/hr/mL)	F[h] (%)	*n*
3	3.87	4.5	0.41	1.78	1.47 (0.32)	4	3.9	1.59 (0.23)	2.0	11.14 (2.23)	66.7 (13.4)	4
16r	3.87	1.5	0.08	0.42	0.85 (0.12)	3		0.51 (0.12)	1.3	2.38 (0.61)	10.3 (2.6)	7
	10.0							0.84 (0.30)	0.9	2.83 (0.75)	4.8 (1.2)[i]	4
	23.4							1.47 (0.28)	1.1	6.65 (0.81)	4.8 (0.6)[i]	4
32c	0.1						≤12	0.49 (0.13)	1.3	8.21 (1.10)	97.9 (13.1)[j]	4
	0.3	9.5	0.04	0.17	0.07 (0.01)	3	>12	1.35 (0.10)	1.4	24.44 (2.62)	97.2 (10.4)	8
	1.0	7.1	0.04	0.13	0.07 (0.01)	6	6.9	2.77 (0.54)	0.9	28.87 (7.69)	34.9 (9.3)	6
	3.0	6.6	0.04	0.12	0.07 (0.01)	3	5.7	9.60 (0.98)	0.9	90.15 (32.25)	36.3 (13.0)	3

[a] $t_{1/2}\beta$, terminal elimination half-life. [b] V_1, volume of distribution of the central compartment (= dose ÷ the plasma concentration at time zero). [c] V_β, volume of distribution of the terminal phase (= CL_p ÷ plasma elimination rate constant). [d] CL_p, total plasma clearance (= dose ÷ area under the curve, mean (SEM). [e] C_{max}, observed peak plasma concentration, mean (SEM). [f] T_{max}, time of peak plasma concentration. [g] AUC, area under the curve, mean (SEM). [h] F, apparent bioavailability of the oral dose. [i] Bioavailability calculated from the 3.87 mg/kg intravenous dose. [j] Bioavailability calculated from the 0.3 mg/kg intravenous dose.

excess of 90% were observed in the 0.1 and 0.3 mg/kg dose groups, decreasing to ~35% at doses ≥1 mg/kg.

Compound **3** was characterized by a plasma elimination half-life (4.5 h) intermediate between compounds **16r** and **32c**. The volume of distribution values for compound **3** were 5–10 times greater than for compounds **16r** and **32c**. Due in part to the higher volume of distribution and plasma clearance values, the peak plasma concentrations for compound **3** were more than 7 times *lower* than those recorded for a 3 mg/kg oral dose of A-81988 (**32c**) in rat. A-81988 has a greater than 20-fold higher area under the curve than compound **3** after iv dosing in rat.

Conclusion

We have discovered a novel series of potent, orally acting angiotensin II antagonists with high bioavailability typified by A-81988 (**32c**). Its unique structural feature is the presence of an alkylamino group linking the heterocyclic ring to the biphenylyltetrazole moiety. Other six-membered ring heterocycles were also active if the ring nitrogen and the carboxylic acid are both situated ortho to the alkylamino group. All substitutions on the pyrimidine ring led to less active compounds. The carboxyl could be

replaced by other strongly acidic groups with slight loss in in vitro activity, but replacement by neutral groups led to a loss of activity.

Experimental Section

General. Flash chromatography was done using silica gel (230–400 mesh) from E.M. Science. Proton NMR spectra were recorded on a General Electric QE300 instrument with Me_4Si as an internal standard. Structure determination by X-ray crystallography was done on a Rigaku ASC-5 instrument. Elemental analyses were performed at Abbott Laboratories. Melting points were measured on a Thomas Hoover apparatus and are uncorrected.

2-(Triphenylmethyl)-5-[(4′-(azidomethyl)biphenyl-2-yl)]-2*H*-tetrazole (11). 2-(Triphenylmethyl)-5-[(4′-(bromomethyl)biphenyl-2-yl)]-2*H*-tetrazole (10)[12] (3.909 g, 7.02 mmol), was dissolved in 11 mL of DMF. Sodium azide (1.16 g, 17.8 mmol) was added and the mixture stirred 16 h at room temperature. Water was added to give a solid which was filtered, dissolved in chloroform, dried (Na_2SO_4), and concentrated, and the residue was crystallized from ether and hexane to give 3.25 g (89% yield) of the title compound, mp 142–145 °C.

2-(Triphenylmethyl)-5-[(4′-(aminomethyl)biphenyl-2-yl)]-2*H*-tetrazole (13). Compound 11 (1.0 g, 1.93 mmol) in 14 mL of THF at 0 °C was treated with $LiAlH_4$ (0.173 g). After 30 min the reaction was worked up with 0.5 mL of water and 0.5 mL of 15% NaOH in the usual manner to give the title compound which was used as is.

2-(Triphenylmethyl)-5-[(4′-[(butylamino)methyl]biphenyl-2-yl)]-2*H*-tetrazole (12, R′ = C_4H_9). To 2-(triphenylmethyl)-5-[(4′-(bromomethyl)biphenyl-2-yl)]-2*H*-tetrazole (6.00 g, 10.7 mmol), dissolved in 55 mL of THF, was added 40 mL of butylamine. After 2 h at room temperature, the mixture was concentrated. The residue was dissolved in $CHCl_3$, washed with dilute KOH and dried (K_2CO_3), and the solvents were removed to give the title compound which was used without further purification.

Ethyl 2-Chloropyridine-3-carboxylate (29, R = H, R″ = C_2H_5). 2-Chloropyridine-3-carboxylic acid (25 g) was refluxed 3 h in 200 mL of benzene and 150 mL of $SOCl_2$. The solution was concentrated and chased with toluene. The residue obtained was refluxed in 100 mL of ethanol for 20 min. The solvents were removed in vacuum to give the product which was used in the next step.

Ethyl 2-(Propylamino)pyridine-3-carboxylate (30, R = H, R′ = C_3H_7, R″ = C_2H_5). The above chloro ester (7.00 g) was heated in a bomb with 12 mL of propylamine and 32 mL of ethanol for 6 h at 100 °C. The solution was concentrated, and the residue was dissolved in toluene, washed with dilute NaOH, dried (Na_2SO_4), concentrated, and chromatographed, (8% EtOAc in hexane) to give 5.07 g of product in 68% yield.

Ethyl 2-[*N*-Propyl-*N*-[[2′-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]amino]pyridine-3-carboxylate (31, R = H, R′ = C_3H_7, R″ = C_2H_5). Ethyl 2-(propylamino)pyridine-3-carboxylate (1.41 g, 6.78 mmol) in 3 mL of THF containing 2 mL of DMPU (1,3-dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone) was treated at 0 °C with 6.78 mL of 1 M LiN(TMS)$_2$ in THF. After 10 min, 3.55 g (6.35 mmol) of bromomethyl compound 10 in 8 mL of THF was added dropwise. After 90 min at room temperature, toluene was added, along with 1 drop of concentrated HCl. The mixture was washed with water three times, dried (Na_2SO_4), and concentrated. The residue was chromatographed, (2.5% ether in toluene) to give 2.55 g of product, mp 129–131 °C (53% yield).

Method A. Removal of the Triphenylmethyl Group on the Tetrazole. Ethyl 2-[*N*-Propyl-*N*-[[2′-(1*H*-tetrazol-5-yl)-biphenyl-4-yl]methyl]amino]pyridine-3-carboxylate (32, X = COOEt, R = H, R′ = C_3H_7). The above triphenylmethyl compound (2.00 g, 2.92 mmol) was dissolved in 24 mL of CH_2Cl_2 and 36 mL of 88% HCOOH for 2 h at room temperature. The solvents were removed in vacuum, and the residue was stirred with 50% HCOOH. The resulting solid (triphenylmethanol) was filtered and washed with 50% HCOOH. The filtrate was concentrated and treated with water. This mixture was extracted with $CHCl_3$. The $CHCl_3$ was dried (Na_2SO_4) and concentrated, and the residue was crystallized from ether to give 1.09 g (87%) of the desired compound, mp 143–144 °C.

Method B. Hydrolysis of Heterocyclic Esters. 2-[*N*-Propyl-*N*-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]pyridine-3-carboxylic Acid (32c, X = COOH, R = H, R′ = C_3H_7). The ethyl ester above (0.400 g, 0.905 mmol) was refluxed 90 min in 10 mL of ethanol and 2 mL of water containing 0.286 g of NaOH. Acetic acid (0.7 mL) was added, and the solution was concentrated. Water containing 0.7 mL of HCOOH was added, and the mixture was dissolved in $CHCl_3$. This was dried (Na_2SO_4) and concentrated, and the residue was crystallized from ether to give 0.278 g of product, mp 202–204 °C in 75% yield. ^1H NMR (DMSO-d_6, 300 MHz): 0.73 (t, J = 7 Hz, 3H), 1.50 (m, 2H), 3.22 (q, J = 7 Hz, 2H), 4.67 (s, 2H), 6.80 (dd, J = 8, 4 Hz, 1H), 7.11 (d, J = 8 Hz, 2H), 7.21 (d, J = 8 Hz, 2H), 7.50–7.70 (m, 4H), 7.86 (dd, J = 4, 2 Hz, 1H), 8.21 (dd, J = 4, 2 Hz, 1H). Anal. ($C_{23}H_{22}N_6O_2$) C, H, N.

Pyrimidines with NH side chains can be hydrolyzed using this method, at room temperature, in 1 h. The pyrimidines unsubstituted in the 2-position, but having an *N*-alkyl, gave an unidentified impurity when hydrolyzed in refluxing EtOH–H_2O, but this was largely eliminated by carrying out the hydrolysis in water at room temperature for 24 h.

Ethyl 2-*n*-Butyl-4-[*N*-[[2′-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]amino]pyrimidine-5-carboxylate (14, R = C_4H_9, R′ = H). Ethyl 2-butyl-4-chloropyrimidine-5-carboxylate[11] (0.40 g, 1.65 mmol) was added to 13 dissolved in 4 mL of THF containing 0.5 g of triethylamine. After 2 h, $CHCl_3$ was added, the solution washed with $NaHCO_3$, dried (Na_2SO_4), and concentrated, and the residue chromatographed, eluting with 10% EtOAc in toluene to give 0.927 g of the title compound, crystallized from ether, mp 116–118 °C (69% yield). All other analogs of 14 could be prepared by this method, including *N*-alkyl compounds.

2-Methoxypropionamidine Hydrochloride. Methyl 2-methoxypropionimidate hydrochloride[16] (53 g, 0.345 mol) in 400 mL of MeOH containing 70 mL of liquid NH_3 was kept at 25 °C for 16 h in an autoclave. The reaction mixture was concentrated, and the residue obtained was dissolved in 2-propanol and filtered from a small amount of insoluble material. The filtrate was concentrated and the residue crystallized from ether to give 47 g of the title compound.

Ethyl 2-(2-Methoxyethyl)-4-hydroxypyrimidine-5-carboxylate. To the above amidine (0.345 mol) dissolved in 200 mL of EtOH and cooled in ice was added slowly 223 g of a 21% solution of NaOEt in EtOH, followed by slow addition of 74.6 g (0.345 mol) of diethyl ethoxymethylene malonate. The solution was refluxed 2 h and then concentrated. Water was added, and the solution was neutralized with HCl and extracted with $CHCl_3$ four times. The organic extracts were dried ($MgSO_4$) and concentrated, and the residue was crystallized from ether to give 58.5 g of the title product, mp 115–118 °C (75% yield).

Ethyl 2-(2-Methoxyethyl)-4-[*N*-[[2′-[2-(triphenylmethyl)-2*H*-tetrazole-5-yl]biphenyl-4-yl]methyl]amino]pyrimidine-5-carboxylate (14, R = $MeOCH_2CH_2$, R′ = H). To the above hydroxypyrimidine (1.85 g, 8.14 mmol) in 13 mL of CH_2Cl_2, containing 1.38 mL of Et_3N, was added 1.025 g (8.96 mmol) of CH_3SO_2Cl with ice cooling. After 5 min of stirring a solution of 4.00 g (8.11 mmol) of 13 and 1.38 g of Et_3N in 5 mL of $CHCl_3$ were added. After 1.5 h of stirring at room temperature, 50 mL of CH_2Cl_2 was added and the solution was washed with $NaHCO_3$, dried ($MgSO_4$), and concentrated. The residue was chromatographed (25% EtOAc in toluene) to give 4.615 g of the title compound, mp 128–130 °C (80% yield).

Ethyl 3-Methyl-5-chloro-1,2,4-triazine-6-carboxylate. To 3-methyl-5-hydroxy-1,2,4-triazine-6-carboxylate[13] (1.50 g, 8.20 mmol), suspended in 12 mL of $POCl_3$, was added 0.827 g (8.20 mmol) of Et_3N. After 1 h of stirring at room temperature, the mixture was concentrated, toluene was added, and the mixture was concentrated again. More toluene was added, and the solution washed with dilute $NaHCO_3$, dried ($MgSO_4$), and concentrated. The residue was dissolved in heptane, filtered from a small amount of insoluble material, and concentrated to give 1.30 g (6.47 mmol) of the title compound in 79% yield.

Ethyl 3-Methyl-5-[*N*-propyl-*N*-[[2′-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]amino]-1,2,4-triazine-6-carboxylate (19). To a solution of compound 12 (R′ = C_3H_7)

(3.14 g, 5.87 mmol) in 8.5 mL of THF, containing 3.1 mL of Et_3N, was added 1.30 g (6.47 mmol) of ethyl 3-methyl-5-chloro-1,2,4-triazine-6-carboxylate, prepared above. After 2 h of stirring at room temperature, the mixture was concentrated. The residue was dissolved in toluene, washed with $NaHCO_3$, dried (Na_2SO_4), and concentrated. The residue was chromatographed (25% EtOAc in toluene) to give 3.91 g (95% yield) of the title compound, mp 178–179 °C.

2,6-Dichloropyridazine-4-carboxylic acid. 2,6-Dichloro-4-methylpyridazine[17] (10 g, 60 mmol) in 60 mL of concentrated H_2SO_4 was treated with powdered $K_2Cr_2O_7$ (21.2 g, 72 mmol), keeping the temperature between 35–40 °C. After 2 h, the mixture was poured into ice and extracted with 1 L of ether. The extracts were washed with brine, dried (Na_2SO_4), and concentrated, and the residue was crystallized from boiling water to yield 8.1 g of the title compound.

Ethyl 2,6-Dichloropyridazine-4-carboxylate. 2,6-Dichloropyridazine-4-carboxylic acid (7.1 g, 37 mmol) in 40 mL of THF with 5 mL of EtOH was treated with 500 mg of (dimethylamino)pyridine and 7.8 g (40 mmol) of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride and stirred overnight at room temperature. The mixture was concentrated and partitioned between water and EtOAc. The organic phase was washed with water, $NaHCO_3$, and NaCl, dried (Na_2SO_4), and concentrated. The residue was chromatographed (3:1 hexane/EtOAc) to give 5.00 g (61% yield) of the title compound.

Ethyl 3-[*N*-Butyl-*N*-[[2′-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]amino]-6-chloropyridazine-4-carboxylate (22). The above ester (520 mg, 2.35 mmol), compound 12 (R′ = C_4H_9) (1.26 g, 2.30 mmol), and 0.42 mL (3.0 mmol) of Et_3N were refluxed together overnight. The reaction mixture was worked up as described for compound 19 and chromatographed (3:1 hexane/EtOAc) to give 1.35 (78%) of the title compound as an amorphous solid.

Ethyl 3-[*N*-Butyl-*N*-[[2′-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]amino]pyridazine-4-carboxylate (22, des chloro). Compound 22, above, (610 mg, 0.83 mmol) was dissolved in 4:1 EtOAc/EtOH containing 140 mg of 10% Pd/C and 0.175 mL of Et_3N (1.26 mmol). It was hydrogenated at atmospheric pressure for 24 h. The product was chromatographed (EtOAc in hexane) to give 260 mg of the title compound.

Ethyl 2-Hydroxy-6-methylpyrazine-3-carboxylate (25). Hydrogen chloride gas was bubbled 15 min through a mixture of 2-hydroxy-6-methylpyrazine-3-carboxylic acid[22] (32.5 g) suspended in 500 mL of EtOH and cooled in ice. This was stirred at room temperature overnight and then refluxed 2 h. The mixture was concentrated and the residue crystallized from ethanol in ether to give 21.48 g (58%) of 25, mp 153 °C.

Ethyl 6-Methyl-2-[*N*-propyl-*N*-[[2′-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]amino]pyrazine-3-carboxylate (26, R = CH_3, R′ = C_3H_7). To ester 25 (1.43 g, 7.86 mmol) in 8 mL of DMF, containing 1.8 g of Et_3N, was added 1.45 g (8.21 mmol) of benzenesulfonyl chloride. After 5 min at room temperature 3.89 g (7.17 mmol) of 12 (R′ = C_3H_7) in 3 mL of toluene was added, and the mixture stirred for 18 h at 45 °C. Dilute $KHCO_3$ was added, and the mixture was extracted with toluene. The product was purified by chromatography (16% EtOAc in toluene) to give 3.00 g (60%) of the title compound.

Methyl 3-[*N*-Butyl-*N*-[[2′-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]amino]pyrazine-2-carboxylate (26, R = H, R′ = C_4H_9). Compound 27[23] (320 mg, 1.47 mmol), compound 12 (R′ = C_4H_9) (825 mg, 1.50 mmol), and Et_3N (0.225 g, 2.22 mmol) in 1.5 mL of THF were refluxed together for 5 h. The usual workup and purification by chromatography (3:1 hexane/EtOAc) gave 708 mg (70%) of the title compound.

Methyl 2-[*N*-Propyl-*N*-[[2′-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]amino]-6-fluoropyridine-3-carboxylate (31, R = 6-F, R′ = C_3H_7, R″ = CH_3). Methyl 2,6-difluoronicotinate[14] (86 mg, 0.5 mmol), compound 12 (R′ = C_3H_7) (272 mg as the formate salt), and Et_3N (0.14 mL, 1 mmol) were refluxed together overnight in 3 mL of THF. The residue, on workup, was chromatographed (20% EtOAc in hexane) giving 200 mg of product in 58% yield. ^1H NMR ($CDCl_3$, 300 MHz): 0.76 (t, J = 7 Hz, 3 H), 1.53 (dt, J = 7, 6.5 Hz, 2H), 3.22 (t, J = 7 Hz, 2H), 3.78 (s, 3H), 4.51 (s, 2H), 6.24 (dd, J = 9, 5 Hz, 1H), 6.85–6.95 (m, 6H), 6.95–7.10 (m, 4H), 7.20–7.50 (m, 11H), 7.90 (dd, J = 2, 7 Hz, 1H), 8.02 (dd, J = 9, 9 Hz, 1H).

2-[*N*-Propyl-*N*-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]-6-fluoropyridine-3-carboxylic Acid (32u) and 2-[*N*-Propyl-*N*-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]-6-methoxypyridine-3-carboxylic Acid (32w). The trityl group was removed from 150 mg (0.218 mmol) of compound 31 (R = 6-F, R′ = C_3H_7, R″ = CH_3) using method A (above). The resulting product was refluxed for 2 h with 3 mL of 1:1 THF/MeOH and 1 mL of 4 N NaOH. The mixture was worked up according to method B, and the products were separated by preparative HPLC using a C_{18} column, giving 17 mg of each compound.

Ethyl 2-Chloro-5-fluoro-6-(methylthio)pyridine-3-carboxylate (35). Ethyl 2,6-dichloro-5-fluoropyridine-3-carboxylate[15] (34, 1.00 g, 8.40 mmol) was stirred 3 h at room temperature with 589 mg (8.40 mmol) of $NaSCH_3$ in 4 mL of water and 4 mL of THF to give the title compound as a white solid. The structure was determined by X-ray crystallography.

Ethyl 2-Chloro-5-fluoropyridine-3-carboxylate (29, R = 5-F). Compound 35 (960 mg, 3.86 mmol) was refluxed 24 h with Raney nickel in EtOH. The product was chromatographed (5% EtOAc in hexane) to give 233 mg (30%) of the desired compound.

Ethyl 5-Fluoro-2-[*N*-propyl-*N*-[[2′-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]amino]pyridine-3-carboxylate (31, R = 6-F, R′ = C_3H_7, R″ = C_2H_5). Compound 29 (R = 5-F) (157 mg, 0.775 mmol) and 415 mg (0.775 mmol) amine 12 (R′ = C_3H_7) were refluxed 18 h with 0.27 mL of Et_3N, in 0.6 mL of THF, and worked up as before to give 59 mg (11%) of the title compound.

Ethyl 2-Bromo-5-methylpyridine-3-carboxylate (29, R = 5-CH_3, R″ = C_2H_5, 2-Br Analog). A modification of the procedure of Baldwin[18] was used. $C_2H_5CH{=}C(CN)COOEt$ (10.6 g, 69 mmol) in 50 mL of EtOH was treated dropwise with 9 mL (69 mmol) of DMF dimethyl acetal, and refluxed 18 h. The solvent was evaporated, and the residue was dissolved in 50 mL of acetic acid. HBr (100 mL, 30% in acetic acid) was added dropwise at 40 °C, and the mixture was heated at 60 °C for 5 h. The solvents were evaporated, the residue basified with $NaHCO_3$ and extracted with EtOAc, and the product chromatographed (25% EtOAc in hexane) to give 2.50 g (15%) of title compound. This compound and the 4-methyl analog were reacted with propylamine and with 10 by the same method as the 2-Cl nicotinates.

2-Hydroxy-5-nitropyridine-3-carboxylic acid (37). Nitric acid (3 mL) was added dropwise to 7.0 g of 2-hydroxynicotinic acid in 50 mL of sulfuric acid at 0 °C. The solution was stirred at room temperature 16 h and at 50–70 °C 1.5 h. Pouring the mixture on to ice gave 7.3 g (87%) of 37.

Ethyl 2-Chloro-5-nitropyridine-3-carboxylate (29, R = 5-NO_2). A 5.00-g sample of the above hydroxy compound was refluxed 2 h with 32 mL of thionyl chloride containing 2 mL of DMF. The solution was concentrated, and the residue was treated with 20 mL of ethanol to give 5.04 g (81%) of the desired compound. This compound reacted with amine 12 at room temperature in 3 h.

Methyl 2-Hydroxy-5-iodopyridine-3-carboxylate (38). Methyl 2-hydroxynicotinate (1.7 g, 11.1 mmol) and 3.25 g (14.4 mmol) *N*-iodosuccinimide were refluxed in 40 mL of CH_2Cl_2 in the dark for 48 h. The solution was washed with sodium thiosulfate twice, brine once, and dried (Na_2SO_4) to give 2.79 g (90%) of 38.

Methyl 2-Chloro-5-iodopyridine-3-carboxylate (29, R = 5-I, R″ = CH_3). Compound 38 (500 mg) was refluxed 7 h in 5 mL of $POCl_3$. Working up the reaction in the usual manner and purifying the product by chromatography (10% EtOAc in hexane) gave 368 mg (69%) of the title compound.

This compound reacts with 12 by refluxing in THF with Et_3N overnight to give 31 (5-I) in 40% yield.

Methyl 5-Phenyl-2-[*N*-propyl-*N*-[[2′-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]amino]pyridine-3-carboxylate (31, R = 5-C_6H_5, R″ = CH_3, R′ = C_3H_7). To a solution of 5 mg of $(Ph_3P)_4Pd$ in 2 mL of toluene was added 48 mg (60 μmol) of 31 (R = 5-I). After 10 min of stirring, 2 mL of nitrogen-sparged 2 N Na_2CO_3 solution was added, followed by 9 mg (70 μmol) of phenylboronic acid (all with careful exclusion of air). The mixture was refluxed 2 h, cooled, and partitioned between ether and water. The organic layer was washed with 1 N H_3PO_4 and then NaCl, dried (Na_2SO_4), and concentrated. The

product was chromatographed (20% EtOAc in hexane) to give the title compound.

Methyl 2,5-Dichloropyridine-3-carboxylate (29, R = 5-Cl, R′ = CH_3). 2-Hydroxynicotinic acid (13.9 g, 0.10 mol) was added to an ice-cooled solution of sodium hypochlorite (170 mL, 0.12 mol) and 32 g of 50% NaOH, and stirred overnight at room temperature. Sodium sulfite (1.4 g) in 5 mL of water was added, and the mixture was acidified with 50 mL of concentrated HCl. The resulting solid was filtered, washed with water and then acetone, and dried in vacuo at 65 °C overnight to give 14.2 g of 5-chloro-2-hydroxynicotinic acid. This acid (5.00 g, 0.029 mol) was refluxed 2 h with 32 mL of thionyl chloride and 2 mL of DMF. The mixture was concentrated and treated with 25 mL of MeOH. After workup the product was purified by chromatography (10% EtOAc in hexane) to get 4.15 g (70%) of the title compound.

This compound was reacted with propylamine and then with 10 by the same method that was used with ethyl 2-chloronicotinate.

Methyl (and Benzyl) 6-Benzyl-2-[*N*-propyl-*N*-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]pyridine-3-carboxylate (32, R = 6-$C_6H_5CH_2O$-, R′ = C_3H_7, X = COOEt). Benzyl alcohol (142 mg, 1.31 mmol) was converted to its sodium salt by stirring with 56 mg of 60% dispersion of NaH (1.40 mmol) in 0.6 mL of DMF for 1 h at room temperature. A solution of the 6-F compound (**32u**, methyl ester, 146 mg, 0.327 mmol) in 1.4 mL of DMF was added. The mixture was stirred at 25 °C for 18 h and at 60 °C for 6 h. The solvent was removed under high vacuum, and the residue was partitioned between 10 mL of 0.1 M $NaHSO_4$ and 20 mL of CH_2Cl_2. The product was purified by chromatography (EtOAc/hexane 1:2) to give 113 mg of an equal mixture of methyl and benzyl esters.

6-Hydroxy-2-[*N*-propyl-*N*-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]pyridine-3-carboxylic Acid (32x). The above mixture of esters (110 mg, 0.188 mmol) was hydrolyzed with 0.75 mL of aqueous NaOH in 2 mL of methanol at 70 °C for 18 h to give 75% of the 6-(benzoyloxy) carboxylic acid. This was hydrogenated over 10% Pd/C (35 mg) in 5 mL of EtOAc and 0.7 mL of Et_3N for 27 h at 1 atm H_2. The product was purified by preparative TLC (5% MeOH, 1% HOAc in CH_2Cl_2) to give 20.3 mg (41%) of **32x**.

Ethyl 5-Amino-2-[*N*-propyl-*N*-[[2′-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]amino]pyridine-3-carboxylate (31, R = 5-NH_2, R′ = C_3H_7, R″ = C_2H_5). Compound **31** (R = 5-NO_2) (500 mg, 0.69 mmol) in 5 mL of EtOAc was hydrogenated at 1 atm for 10 h over 75 mg 10% Pd/C to give 395 mg (82%) of the title compound.

Ethyl 5-(Acetylamino)-2-[*N*-propyl-*N*-[[2′-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]amino]pyridine-3-carboxylate (31, R = 5-AcNH, R′ = C_3H_7, R″ = C_2H_5). Compound **31** (R = 5-NH_2) (50 mg) was stirred overnight with 1 mL of $CHCl_3$, 0.1 mL of Et_3N, and 0.2 mL of acetic anhydride. Workup and purification by chromatography (25% EtOAc in hexane) gave the title compound.

Methyl 4-[*N*-Propyl-*N*-[[2′-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]amino]pyridine-3-carboxylate (41). 4-Chloronicotinic acid[19] was converted to the methyl ester (**40**) in 85% yield with diazomethane. This ester (700 mg, 4.08 mmol), amine **12** (R = C_3H_7), and Et_3N (1.1 mL, 7.89 mmol) in 10 mL of 2-propanol were heated in a sealed tube at 120 °C for 6 h. The product was worked up as described for the 2-amino isomer to give 454 mg (25%) of **41**.

Ethyl 2-[*N*-Butyl-*N*-[[2′-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]amino]pyridine-5-carboxylate (44, R′ = C_4H_9). 6-Chloronicotinic acid was esterified by the method used for 2,6-dichloropyridazine-4-carboxylate, described above. This chloro ester was reacted with butylamine by the method used for ethyl 2-chloronicotinate, and the resulting ethyl 6-(butylamino)nicotinate reacted with **10** in a similar manner to give the title compound in 67% yield.

Ethyl 3-(Propylamino)pyridine-4-carboxylate. 3-Aminopyridine-4-carboxylic acid[20] (2.00 g) was esterified by warming on a steambath with 4 g of ethanol and 4.0 g of H_2SO_4, for 4 h. To this ester (750 mg, 4.52 mmol), in 35 mL of THF containing 1.30 mL of DMPU at 0 °C, was added of 4.7 mL of 1 M lithium hexamethyl disilazide. After 30 min of stirring at 0 °C, 0.80 mL (9.24 mmol) of allyl bromide was added. The mixture was stirred at room temperature overnight and worked up as usual. The product was chromatographed (1:5 EtOAc/hexane) to give 465 mg of the 3-allylamino compound. This was hydrogenated in 25 mL of EtOAc over 55 mg of PtO_2 to give 448 mg of the title compound.

Ethyl 3-[*N*-propyl-*N*-[[2′-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]amino]pyridine-4-carboxylate (47, R = C_3H_7). The 3-propylamino compound described above (405 mg, 1.95 mmol) was alkylated with **10** using the method used to convert **30** to **31**. The product was purified by chromatography, giving 190 mg (14%) of the title compound.

Ethyl 2-(Butylamino)pyrimidine-5-carboxylate (50). Ethyl 2-(ethylthio)pyrimidine-5-carboxylate[21] (974 mg, 4.6 mmol) was heated in a sealed tube for 3 h with 2 mL of butylamine and 4 mL of EtOH. The solution was concentrated, and the residue was partitioned between $NaHCO_3$ solution and EtOAc. The product was purified by chromatography (20% EtOAc in hexane) to give 850 mg of the desired product as a white solid.

Ethyl 2-[*N*-Butyl-*N*-[[2′-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]amino]pyrimidine-5-carboxylate (51). Compound **50** (573 mg, 2.57 mmol) was reacted with 1.43 g (2.57 mmol) of **10** using the method used to convert **30** to **31**. The yield was 1.20 g (67%).

Methyl 2-Chloro-4-[*N*-butyl-*N*-[[2′-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]amino]pyrimidine-6-carboxylate. Methyl 2,4-dichloropyrimidine-6-carboxylate[31] (220 mg, 1.06 mmol), 1 mL of Et_3N, amine **12** (R = C_4H_9) (495 mg, 0.90 mmol), and 2 mL of DMF were stirred at 25 °C for 15 min. The mixture was dissolved in EtOAc, washed with brine, dried (Na_2SO_4), and concentrated. The product was purified by chromatography (3% EtOAc in CH_2Cl_2) to give 500 mg of the title compound.

4-[*N*-Butyl-*N*-[[2′-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]amino]pyrimidine-6-carboxylic Acid (55, R′ = C_4H_9). The 2-chloropyrimidine synthesized above (880 mg, 1.2 mmol) in 8 mL of THF was hydrogenated over 1.30 g of 10% Pd/C at 1 atm for 24 h. The triphenylmethyl group was removed, and the ester was hydrolyzed as described by the general methods A and B to give 185 mg (40%) of the title compound. NMR showed that the compound was a 4-aminopyrimidine rather than a 2-aminopyrimidine. NMR (DMSO-d_6): 0.90 (t, J = 7.5 Hz, 3H), 1.30 (m, 2H), 1.50 (m, 2H), 3.55 (bs, 2H), 4.87 (bs, 2H), 7.05 (d, J = 8 Hz, 2H), 7.15 (d, J = 8 Hz, 2H), 7.52–7.68 (m, 4H), 7.62 (s, 1H), 8.60 (s, 1H).

Ethyl 1-(Butylamino)benzene-2-carboxylate. Ethyl anthranilate (4.96 g, 30 mmol), K_2CO_3 (13.8 g, 100 mmol), and butyl iodide (25 mL) were stirred at room temperature 48 h and then refluxed 8 h. The mixture was diluted with EtOAc, filtered, and concentrated. The residue was chromatographed (EtOAc in hexane) to give 2.20 g (33%) of the desired product as a yellow liquid.

Ethyl 1-[*N*-Butyl-*N*-[[2′-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]amino]benzene-2-carboxylate (57). Ethyl 1-(butylamino)benzene-2-carboxylate (2.00 g, 9.0 mmol), K_2CO_3 (1.38 g, 10 mmol), and **10** (2.00 g, 3.0 mmol) were stirred in 3 mL of DMF at 55 °C for 20 h. The product was chromatographed, (EtOAc in hexane) to get 800 mg (46%) of the title compound.

3-(Hydroxymethyl)-2-[*N*-propyl-*N*-[[2′-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]amino]pyridine (59, X = CH_2OH, R′ = C_3H_7). Ester **31** (R = H, R′ = C_3H_7, R″ = C_2H_5) (2.574 g, 3.758 mmol) in 20 mL of THF at 0 °C was treated with 500 mg (13.2 mmol) of $LiAlH_4$. After 2 h the reaction was subject to a basic workup. The product was chromatographed (22% EtOAc in hexane) to give 2.290 g (95%) of the title compound.

2-[*N*-Propyl-*N*-[[2′-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]amino]pyridine-3-carboxaldehyde (59, X = CHO, R′ = C_3H_7). Alcohol **59** (X = CH_2OH, R′ = C_3H_7) (1.0123 g, 1.575 mmol) and activated manganese dioxide (3.00 g, 34.5 mmol) were stirred at room temperature 20 h. The solids were filtered and the solution concentrated. The residue was chromatographed (20% EtOAc in hexane) to give 0.946 g (96%) of the title compound.

3-(1-Hydroxyethyl)-2-[*N*-propyl-*N*-[[2′-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]amino]pyridine [59, X = $CH(OH)CH_3$, R′ = C_3H_7]. Aldehyde **59** (X = CHO, R′ = C_3H_7) (172.5 mg, 0.269 mmol) in 3 mL of THF was

treated with 1.5 M methylmagnesium bromide in THF (0.27 mL, 0.41 mmol). After 15 min, the reaction was quenched with NH_4Cl. Chromatography (25% EtOAc in hexane) gave 164.5 (93%) of the title compound.

3-Acetyl-2-[*N*-propyl-*N*-[[2′-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]amino]pyridine (59, X = $COCH_3$, R′ = C_3H_7). Alcohol **59** [X = $CH(OH)CH_3$, R′ = C_3H_7) (108.6 mg, 0.163 mmol) in 7 mL of CH_2Cl_2 was added to 1,1,1-tris(acetoxy)-1,1-dihydro-1,2-benziodoxol-3(1H)-one[24] (220 mg, 0.519 mmol). After 30 min of stirring at room temperature, the mixture was chromatographed (20% EtOAc in hexane) to get 65.7 mg (62%) of the title compound.

3-[2-(Ethoxycarbonyl)-1-hydroxyethyl]-2-[*N*-propyl-*N*-[[2′-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]amino]pyridine (59, X = $CH(OH)CH_2COOEt$, R′ = C_3H_7). *n*-Butyllithium in hexane (1.3 M, 0.70 mL, 0.90 mmol) was added to diisopropylamine (0.150 mL, 1.07 mmol) in 8 mL of THF at 0 °C. After 15 min, the mixture was cooled to −78 °C and treated with ethyl acetate (0.090 mL, 0.93 mmol). After 20 min, aldehyde **59** (X = CHO, R′ = C_3H_7) (515 mg, 0.804 mmol) was added and the reaction stirred at −78 °C for 45 min. The reaction was quenched with $NaHCO_3$ solution. Chromatography (30% EtOAC in hexane) gave 556 mg (97%) of the title compound.

***N*-(Benzenesulfonyl)-2-[*N*-propyl-*N*-[[2′-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]amino]pyridine-3-carboxamide (59, X = $CONHSO_2C_6H_5$, R′ = C_3H_7).** Compound **31** (R = H, R′ = C_3H_7, R″ = C_2H_5) was hydrolyzed using method B, without using the HCOOH to give the triphenylmethyl-protected acid. This acid (930 mg, 1.42 mmol) was stirred 1 h at room temperature with 678 mg (5.7 mmol) of thionyl chloride in 2 mL of CH_2Cl_2. The solvents were evaporated and benzene sulfonamide (1.3 g, 8.5 mmol) was added. The reaction was cooled to −78 °C and 2 mL of Et_3N was added, and the mixture was stirred overnight at room temperature. The product was purified by chromatography (1:1 EtOAc/hexane) to give 390 mg (35%) of the title compound.

2-(Butylamino)pyridine-3-carbonitrile. 2-Chloropyridine-3-carbonitrile (1.30 g, 9.60 mmol) was refluxed overnight with 3 mL of *n*-butylamine in 10 mL of isopropyl alcohol. The product was purified by chromatography (2:1 hexane/EtOAc) to give 1.6 g (95%) of the desired product.

2-[*N*-Butyl-*N*-[[2′-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]amino]pyridine-3-carbonitrile (59, X = CN, R′ = C_4H_9). 2-(Butylamino)pyridine-3-carbonitrile (1.60 g, 9.14 mmol) and **10** (5.32 g, 9.55 mmol) were reacted by the method used to convert **30** to **31**. The product was chromatographed (25% ether in hexane) to give 3.60 g (60%) of the title compound.

2-[*N*-Butyl-*N*-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]pyridine-3-carboxamide (32y). Compound **32aa** (100 mg) was refluxed in 3 mL of EtOH and 3 mL of 10% KOH in water, for 16 h. The solution was concentrated, water and HCOOH were added, and the resulting oil was chromatographed (2.5% HCOOH, 2.5% water in EtOAc) to give 55 mg (54%) of the title compound, mp 194–197 °C.

3-(Aminomethyl)-2-[*N*-butyl-*N*-[[2′-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]amino]pyridine (59, X = CH_2NH_2, R′ = C_4H_9). Nitrile **59** (X = CN) (1.52 g, 2.33 mmol) in 50 mL of ether and 0.26 g of $LiAlH_4$ were refluxed 1 h. Basic workup gave 1.20 g (79%) of the title compound which was used directly in the next step.

3-[(Trifluoromethanesulfonamido)methyl]-2-[*N*-butyl-*N*-[[2′-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]amino]pyridine (59, X = $CH_2NHSO_2CF_3$, R′ = C_4H_9). To the aminomethyl compound described above (330 mg, 0.504 mmol), in 20 mL of CH_2Cl_2 containing 0.13 g of 2,6-di-*tert*-butyl-4-methylpyridine, cooled to −20 °C, was added 0.11 mL (0.655 mmol) of trifluoromethanesulfonic anhydride. After 2 h of stirring at −20 °C, the mixture was washed with $NaHCO_3$, and the residue was chromatographed (30% EtOAc in hexane) to get 140 mg (40%) of the title compound.

3-Nitro-2-[*N*-propyl-*N*-[[2′-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]amino]pyridine (59, X = NO_2, R′ = C_3H_7). 2-Chloro-3-nitropyridine (1.29 g, 8.14 mmol) was refluxed 2.5 h with amine **12** (R′ = C_3H_7) (4.03 g, 7.53 mmol) in 8 mL of THF containing 2.5 mL of Et_3N. The solution was concentrated and the residue dissolved in toluene, washed with $NaHCO_3$, and dried (Na_2SO_4). Chromatography (25% EtOAc in toluene) gave 4.35 g (88%) of the title compound, mp 104–106 °C.

3-Amino-2-[*N*-propyl-*N*-[[2′-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]amino]pyridine (59, X = NH_2, R′ = C_3H_7). Compound **59** (X = NO_2) (2.00 g) in 250 mL of EtOAc was hydrogenated over 200 mg of 10% Pd/C at 4 atm for 2 h to give 1.2 g (60%) of the title compound, after chromatography (25% EtOAc in hexane).

3-[[(Methylamino)carbonyl]amino]-2-[*N*-propyl-*N*-[[2′-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]amino]pyridine (59, X = $NHCONHCH_3$, R′ = C_3H_7). Compound **59** (X = NH_2) (630 mg, 1.0 mmol) in 5 mL of CH_2Cl_2 was treated with 65 mg (1.14 mmol) of methyl isocyanate. After stirring overnight, the product was chromatographed (50% EtOAc in hexane) to give 390 mg (50%) of the title compound.

3-(Acetylamino)-2-[*N*-propyl-*N*-[[2′-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]amino]pyridine (59, X = $NHCOCH_3$, R′ = C_3H_7). Compound **59** (X = NH_2) (500 mg, 0.796 mmol) was stirred overnight with 0.30 mL of acetic anhydride in 10 mL of pyridine. The mixture was concentrated and the product chromatographed (20% EtOAc in hexane) to give 400 mg (78%) of the title compound.

3-[(Trifluoroacetyl)amino]-2-[*N*-propyl-*N*-[[2′-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]amino]pyridine (59, X = $NHCOCF_3$, R′ = C_3H_7). Compound **59** (X = NH_2) (100 mg, 0.16 mmol) was stirred for 1 h with 34 μL (0.24 mmol) of trifluoroacetic anhydride and 25.7 μL of pyridine in 5 mL of CH_2Cl_2. The mixture was concentrated and chromatographed (17% EtOAc in hexane) to get 100 mg (86%) of the title compound.

3-Methanesulfonamido-2-[*N*-propyl-*N*-[[2′-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]amino]pyridine (59, X = $NHSO_2CH_3$, R′ = C_3H_7). Compound **59** (X = NH_2) (500 mg, 0.8 mmol) was stirred 18 h with 0.92 mL (1.04 mmol) of methanesulfonyl chloride and 0.11 mL of Et_3N in 10 mL of CH_2Cl_2. Chromatography (25% EtOAc in hexane) gave 30% of the title compound.

3-(Trifluoromethanesulfonamido)-2-[*N*-propyl-*N*-[[2′-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]amino]pyridine (59, X = $NHSO_2CF_3$, R′ = C_3H_7). Compound **59** (X = NH_2) (250 mg, 0.40 mmol) was stirred for 1 h at −20 °C with 84 μL of trifluoromethanesulfonic anhydride and 110 mg of 2,6-di-*tert*-butyl-4-methylpyridine. The mixture was washed with $NaHCO_3$, dried, and concentrated to give the title compound in 70% yield.

3-Thioureido-2-[*N*-propyl-*N*-[[2′-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]amino]pyridine (59, X = $NHCSNH_2$, R′ = C_3H_7). Compound **59** (X = NH_2) (200 mg, 0.329 mmol) in 3.2 mL of THF at −78 °C was treated with 0.335 mL (0.335 mmol) of 1 M sodium hexamethyl disilazide in THF. After 30 min at −78 °C, 40 mg (0.350 mmol) thiophosgene was added. The red solution was stirred for 30 min at 0 °C and then treated with aqueous ammonia. This mixture was stirred 30 min at room temperature. The solution was concentrated, and the residue was partitioned between CH_2Cl_2 and water. The product was purified by chromatography (40% EtOAc in hexane) to give 160 mg (73%) of the title compound.

3-[[(Ethoxycarbonyl)carbonyl]amino]-2-[*N*-propyl-*N*-[[2′-[2-(triphenylmethyl-2*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]amino]pyridine (59, X = $NHCOCOOEt$, R′ = C_3H_7). Compound **59** (X = NH_2) (150 mg, 0.24 mmol), in 6 mL of CH_2Cl_2 containing 0.1 mL of Et_3N, at 0 °C, was treated with 54 mg (0.48 mmol) of ethyl oxalyl chloride and stirred 2 h. The mixture was concentrated, and the residue was chromatographed (15% EtOAc in hexane) to give 149 mg (85%) of the title compound. In the preparation of the diacid **32ww**, the ester hydrolysis (method B) was carried out at room temperature for 18 h.

3-(Benzyloxy)-2-(butylamino)pyridine (64). To 2-amino-3-(benzyloxy)pyridine (**63**, Aldrich, 2.50 g, 12.5 mmol) in THF at 0 °C was added 12.5 mL of 1 M lithium hexamethyl disilazide in THF. After 30 min at room temperature, 2.30 g (12.5 mmol) of *n*-butyl iodide was added and the mixture stirred overnight at room temperature. After workup, the product was purified by chromatography (10% EtOAc in hexane) and gave 2.75 g (86%) of the title compound.

3-(Benzyloxy)-2-[*N*-butyl-*N*-[[2′-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]amino]pyridine (59, X = $OCH_2C_6H_5$, R′ = C_3H_7). Compound **64** (1.35 g, 5.3 mmol) was reacted with **10** (3.54 g, 5.3 mmol) by the same method as **64** itself was prepared (above). The product was purified by chromatography (10% EtOAc in hexane) to give 2.40 g (62%) of the title compound.

3-Hydroxy-2-[*N*-butyl-*N*-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]pyridine (32kk). The compound above was detritylated by method A in 76% yield. This compound (200 mg, 0.41 mmol) was hydrogenated for 7 h at 1 atm at room temperature in 100 mL of EtOAc containing 3 mL of Et_3N, using 100 mg of 10% Pd/C as catalyst. The product was purified by chromatography (5% MeOH, 0.5% AcOH, in $CHCl_3$) to get 158 mg (96%) of **32kk**.

3-Acetoxy-2-[*N*-butyl-*N*-[[2′-(1*H*-tetrazol-5-yl]biphenyl-4-yl]methyl]amino]pyridine (32pp). Compound **32kk** (75 mg, 0.19 mmol) in 2 mL of DMF and 2 mL of pyridine was treated with 2 drops of acetic anhydride. After 1 h of stirring at room temperature, the solution was concentrated, dissolved in ether, washed with water, dried (Na_2SO_4), and concentrated to give 41 mg (53%) of **32pp**.

3-[[(Methylamino)carbonyl]oxy]-2-[*N*-butyl-*N*-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]pyridine (32mm). To compound **32kk** (32 mg, 0.08 mmol), in 1 mL of DMF and 0.2 mL of Et_3N, were added two drops of methyl isocyanate. After 2 h, the solution was concentrated and the residue chromatographed (5% MeOH, 0.5% AcOH in $CHCl_3$) to get 16 mg (49%) of **32mm**.

2-[*N*-Butyl-*N*-[[2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]pyridine-3-yl Phosphate (32nn). Compound **32kk** (25 mg, 0.06 mmol) was stirred 2.5 h with 0.5 mL of pyridine and 3 drops of $POCl_3$. After cooling to 0 °C, 10 drops of water and 3 drops of 1 N NaOH were added, and then the solution was stirred at room temperature for 1 h. The product was purified by reverse-phase HPLC, eluting with a gradient of 0 to 70% acetonitrile in 0.1% aqueous trifluoroacetic acid to afford 4 mg (15%) of **32nn**.

2-[*N*-Butyl-*N*-[[2′-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]-biphenyl-4-yl]methyl]amino]-4,6-dimethylpyrimidine (Trityl 67). 2-(Butylamino)-4,6-dimethylpyrimidine[25] (968 mg, 5.41 mmol) was reacted with **10** (2.52 g, 4.52 mmol) using the method used to convert **30** to **31**. The product was purified by chromatography (2% ether in toluene), giving 1.65 g (55%) of the title compound, mp 131–133 °C.

4-[*N*-Butyl-*N*-[[2′-[2-(triphenylmethyl)-2*H*-tetrazol-5-yl]-biphenyl-4-yl]methyl]amino]-2,6-dimethylpyrimidine (Trityl 65). 4-(Butylamino)-2,6-dimethylpyrimidine[25] (806 mg, 4.50 mmol) was reacted with **10** (2.10 g, 3.76 mmol) using the method used to convert **30** to **31**. The product was purified by chromatography (40% EtOAc in toluene), giving 1.55 g (63%) of the title compound, mp 125–127 °C.

2-[*N*-Propyl-*N*-[[2′-[2-(triphenylmethyl)-tetrazol-5-yl]biphenyl-4-yl]methyl]amino]pyrimidine (Trityl 69). 2-Bromopyrimidine (1.00 g, 6.28 mmol), amine **12** (R′ = C_3H_7) (2.00 g, 3.74 mmol), and diisopropyl ethylamine (1.00 g, 7.75 mmol) were refluxed 10 h in 3.5 mL of acetonitrile. Toluene was added and the mixture washed with $NaHCO_3$, dried (Na_2SO_4), and concentrated. Chromatography (4% EtOH in toluene) gave 1.64 g (71%) of the title compound, mp 133–134 °C.

Methyl 2-[*N*-Propyl-*N*-[(2′-carbomethoxybiphenyl-4-yl)-methyl]amino]pyridine-3-carboxylate (71, R = CH_3). Methyl (2-propylamino)nicotinate (**30**) (194 mg, 1.0 mmol) was reacted with bromide **70**[12] (381 mg, 1.0 mmol); using the same method described above in which **30** was reacted with **10** to give **31**. The product was purified by chromatography (30% EtOAc in hexane) to give 367 mg (88%) of **71** (R = CH_3).

Methyl 2-Hydroxy-6-(benzyloxy)benzoate. 2,6-Dihydroxybenzoic acid was esterified with diazomethane in 60% yield. This ester (500 mg, 2.97 mmol) in 5 mL of THF was added to a suspension of sodium hydride (120 mg of 60% dispersion washed with THF, 2.97 mmol) in 2 mL of THF. After 10 min benzyl bromide (0.354 mL, 2.97 mmol) and 5 mg of tetrabutylammonium iodide were added. After 2 h of refluxing, the solution was added to $NaHCO_3$ solution, and extracted with EtOAc. The product was purified by chromatography (10% ether in hexane) to yield 230 mg (30%) of the title compound.

Methyl 2-Trifloxy-6-(benzyloxy)benzoate (73). To a stirred solution of the above phenol (230 mg, 0.89 mmol), in 1.2 mL of CH_2Cl_2 containing 0.35 (4.45 mmol) pyridine, and cooled to 0 °C, was added 0.18 mL (1.02 mmol) of trifluoromethanesulfonic anhydride. After 30 min at 0 °C and 2 h at room temperature, ether was added and the solution washed with $NaHCO_3$, water, 3 N HCl, and again water and dried ($MgSO_4$). After concentration, the residue was chromatographed (18% ether in hexane) to yield 177 mg (51%) of **73**.

Methyl 2-(Benzyloxy)-4′-methylbiphenyl-2-carboxylate (74). To a stirred solution of **73** (498 mg, 1.26 mmol) in 3 mL of toluene was added 64 mg (0.06 mmol) of $(Ph_3P)_4Pd$. After 10 min, 3 mL of 2M aq. Na_2CO_3 was added followed by a solution of 4-methylphenylboronic acid (256 mg, 1.51 mmol) in 1.5 mL ethanol. The resulting mixture was stirred rapidly under reflux for 1 h. The mixture was cooled to room temperature and phases separated. After concentration, the residue was purified by chromatography (20% ether in hexane) to give 410 mg (96%) of **74**.

Methyl 2-[(*tert*-Butyldimethylsilyl)oxy]-4′-methylbiphenyl-2-carboxylate. Compound **74** (406 mg, 1.22 mmol) was hydrogenated at 1 atm in 4 mL of methanol over 150 mg of 10% Pd/C to give 242 mg (1.0 mmol, 82%) of the 2-hydroxy compound. This was dissolved in 3 mL of CH_2Cl_2, and treated with 2,6-lutidine (174 μL, 1.5 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (252 μL, 1.1 mmol). The mixture was stirred 10 min, diluted with ether, washed with 1 M HCl, water, $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated. The product was chromatographed (5% ether in hexane) to give 315 mg (88%) of the title compound.

Methyl 2-[(*tert*-butyldimethylsilyl)oxy]-4′-(bromomethyl)biphenyl-2-carboxylate. The 4′-methyl compound (above) (312 mg, 0.87 mmol), *N*-bromosuccinimide (156 mg, 0.87 mmol), and AIBN (2 mg) were refluxed 3 h in of CCl_4. The mixture was cooled to room temperature, filtered, and concentrated. The product was chromatographed (5% ether in hexane) to give 284 mg (75%) of the title compound. NMR analysis showed 3% CH_3 and 10% $CHBr_2$ impurities.

Methyl 2-[*N*-Propyl-*N*-[[2′-carbomethoxy-3′-[(*tert*-butyldimethylsilyl)oxy]biphenyl-4-yl]methyl]amino]pyridine-3-carboxylate (75). Compound **30** (R = H, R′ = C_3H_7, R″ = CH_3) (106 mg, 0.55 mmol) was alkylated with the above described bromomethyl compound (280 mg, 0.55 mmol) using the same method used when alkylating with **10**. The product was purified by chromatography (30% EtOAc in hexane) to give 90 mg (30%) of **75**.

2-[*N*-Propyl-*N*-[(2′-carboxy-3′-hydroxybiphenyl-4-yl)-methyl]amino]pyridine-3-carboxylic Acid (76). Compound **75** (40 mg, 0.1 mmol) in 0.5 mL of THF was treated with 0.2 mL (0.2 mmol) of a 1 M solution of tetrabutylammonium fluoride. The mixture was stirred 30 min, poured into brine, extracted with EtOAc, dried (Na_2SO_4), and concentrated to get 31 mg of the diester of **76**. This was refluxed overnight in 1 N NaOH in water, methanol, and THF. After cooling, the mixture was acidified to pH = 2 with 1 N HCl to give 25 mg (86%) of **76**.

Radioligand Binding. The binding of [^{125}I]-Saralasin (NEN) to angiotensin II (type 1) receptors in rat liver was performed as described by S. J. Fluharty.[26] Rat liver membranes were prepared as described by D. M. Nelville Jr.[27] and assayed using 1 μM angiotensin to define nonspecific binding. The binding of [^{125}I]-Tyr^4 angiotensin II (NEN) to type 2 receptors in bovine cerebellum was performed using a kit (NED-001) obtained from New England Nuclear.

Compounds were tested at multiple concentrations as required and analyzed as previously described.[28]

pA_2 Determination in the Rabbit Aorta. The method used was that of Chiu[29] with the exception in that aortic rings were used instead of spiral strips. The pA_2 calculation was done by the method of Schild.[36] For a full pA_2 determination, several doses of the drug was used and a Schild plot (log concentration of drug vs log EC_{50} ratio−1) was made. The EC_{50} ratio equals the EC_{50} of angiotensin II with the drug, divided by the EC_{50} of angiotensin II alone. For competitive antagonists, the slope of this plot should be between 0.90 and 1.15. For an estimated pA_2, (sometimes known as pK_b) the drug was tested at a single concentration of 10^{-7} molar. Then, assuming the slope of the

Schild plot to be 1.00, the estimated $pA_2 = \log(ED_{50}\text{ ratio}-1)/10^{-7} = 7 + \log(EC_{50}\text{ ratio}-1)$.

Oral Antihypertensive Activity in the Renal Artery Ligated Hypertensive Rat Model. The conscious renal hypertensive rat model was used to evaluate the compounds. Male Sprague–Dawley rats (300–350 g) were used, and the method reported by Cangiano et al.[30] for renal artery ligation was employed to induce hypertension. Rats were used on the 6th or 7th day after renal artery ligation. Arterial blood pressure was measured from the indwelling femoral artery catheter. Data of blood pressure and heart rate were determined on line using a Buxco Cardiovascular Analyzer (Buxco Electronics Inc, Sharon, CT).

Oral Antihypertensive Activity in the Furosemide Treated Spontaneously Hypertensive Rat. Male SHR, 20–24 weeks old, were pretreated with furosemide, 10 mg/kg sc, at 22 and 4 h prior to the experiment. Measurements of arterial blood pressure and heart rate were similar to those described for the experiment with the renal artery ligated hypertensive rat.

Pharmacokinetics. The pharmacokinetic behavior of selected A-II antagonists was evaluated in male Sprague–Dawley-derived rats. The A-II antagonists were prepared as solutions in normal saline at concentrations appropriate to provide a 1 mL/kg volume for both intravenous and oral dosing. Each compound was administered as either a slow bolus intravenous dose in the jugular vein or as a oral dose (administered by gavage). Heparinized blood samples (~0.4 mL) were obtained from a tail vein of each rat at 0.1 (iv only), 0.25, 0.5, 1, 2, 4, 6, 9, 12, 15, and 24 h after dosing. The samples were analyzed by reverse-phase HPLC following liquid–liquid extraction from the plasma. Initial estimates of the pharmacokinetic parameters for NONLIN84[33] were obtained with the program CSTRIP.[34] Area under the curve (AUC) values were calculated by the trapezoidal rule over the time course of the study. The terminal-phase rate constant (β) was used in the extrapolation of the AUC from 0 h to infinity (AUC 0–∞). The total plasma clearance (CL_p) was calculated by dividing the dose by the AUC. Assuming dose proportionality and correcting for the differences in dosing, a comparison of the AUC following oral dosing with that obtained following intravenous dosing provided an estimate of the bioavailability (F).

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