Pyrido[2,3-*d*]pyrimidine Angiotensin II Antagonists

John W. Ellingboe,* Madelene Antane, Thomas T. Nguyen, Michael D. Collini, Schuyler Antane, Reinhold Bender, Dale Hartupee, Valerie White, John McCallum, C. Hyung Park, Anthony Russo, Mary B. Osler, Alexandra Wojdan, Joseph Dinish, Douglas M. Ho,† and Jehan F. Bagli

Wyeth-Ayerst Research, Division of Exploratory Chemistry and Division of Cardiovascular and Metabolic Disorders, CN 8000, Princeton, New Jersey 08543-8000

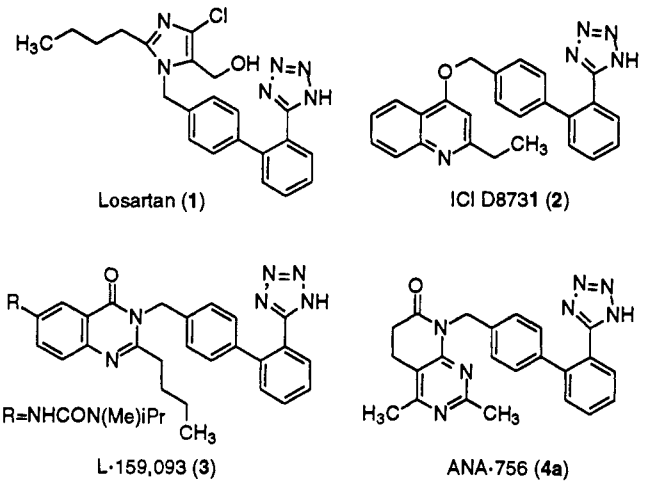
Received October 8, 1993®

A series of pyrido[2,3-*d*]pyrimidine angiotensin II (A II) antagonists was synthesized and tested for antagonism of A II. Compounds with a biphenylyltetrazole pharmacophore and small alkyl groups at the 2- and 4-positions of the pyridopyrimidine ring were found to be the most potent in an AT_1 receptor binding assay and in blocking the A II pressor response in anesthetized, ganglion-blocked A II-infused rats. 5,8-Dihydro-2,4-dimethyl-8-[(2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl)methyl]pyrido[2,3-*d*]pyrimidin-7(6*H*)-one (**4a**) was one of the more potent compounds in the binding assay and was the most efficacious compound in the A II-infused rat model. Further study of **4a** in Goldblatt (2K-1C) rats showed the compound to have oral bioavailability and to be an efficacious and potent compound in a high renin form of hypertension.

The renin-angiotensin system (RAS) plays an important role in the regulation of blood pressure through the actions of angiotensin II (A II) (vasoconstriction, aldosterone secretion, renal sodium reabsorption, and norepinephrine release) and thus is an appropriate target for therapeutic intervention in hypertension.[1] Inhibition and antagonism of the various components of the RAS have been the subject of extensive research, culminating in such drugs as angiotensin converting enzyme (ACE) inhibitors,[2] renin inhibitors,[3] and more recently A II antagonists.[4] ACE inhibitors effectively reduce hypertension but can produce undesirable side effects such as cough and angioedema. ACE inhibitors may interact with enzymes that process bradykinin and substance P to produce such side effects.[5] A II antagonists selectively block A II at the receptor level and should be devoid of the adverse effects associated with ACE inhibitors.

Numerous patents and publications on A II antagonists have appeared in the last several years. The majority of these compounds are selective for the type 1 A II (AT_1) receptor which mediates the blood pressure effects described above. Compounds such as losartan (DuP-753, **1**),[6] ICI D8731 (**2**),[7] and L-159,093 (**3**)[8] are examples of AT_1 selective antagonists (Chart 1). There are a number of structural similarities among many of the reported A II antagonists. Compounds **1–3** contain a biphenylyltetrazole group as a common pharmacophore, which is appended to a heterocyclic ring via a methylene group. The biphenylyltetrazole group is generally associated with the greatest binding affinity at the AT_1 receptor and with the best oral activity in animal models.[6a] Compounds **1–3** bear an alkyl chain on the heterocycle, attached adjacent to a nitrogen (butyl in **1** and **3**, and ethyl in **2**). These alkyl chains may fit into a lipophilic pocket in the AT_1 receptor. An atom capable of serving as a hydrogen-bond acceptor can be found adjacent to the point of attachment of the biphenylyltetrazole group in the heterocyclic portions of **1–3**. The imidazole 3-nitrogen in **1**, the quinoline nitrogen in **2**, and the carbonyl group in **3** are possible hydrogen-bond acceptors.

Chart 1



Utilizing the common structural features outlined above a series of pyridopyrimidine compounds (**4**) was prepared. The synthesis and A II antagonist activity of these compounds are described in this paper.

Chemistry

Compounds with a biphenylyltetrazole group (**4a–m**) were prepared according to method A (Scheme 1). Standard pyrimidine synthesis from a 2-acetylglutarate (**5**) and an amidine (**6**) yielded a pyrimidinone (**7**). The 2-acetylglutarates (**5**) that were not commercially available were prepared by the lithium iodide catalyzed Michael addition of a β-keto ester to an acrylate.[9] Chlorination of **7** with phosphorus oxychloride gave a chloropyrimidine (**8**). Displacement of the chloride with 4-bromobenzylamine, with concomitant cyclization, yielded a pyrido[2,3-*d*]-pyrimidinone (**9**). Palladium-catalyzed coupling[10] of boronic acid **10a** with **9** gave **11** and acid-catalyzed cleavage of the *tert*-butyl protecting group gave the target compound (**4**). Boronic acid **10a** used in the coupling reaction was prepared according to method B (Scheme 2). Reaction of 2-bromobenzonitrile (**12**) with ammonium azide gave (2-bromophenyl)tetrazole (**13**). Protection with a *tert*-butyl group[11] gave compound **14**, which served as a precursor to both **10a** and **10b**. Treatment of **14** with

† Princeton University, Department of Chemistry, Princeton, NJ 08544-1009.

® Abstract published in *Advance ACS Abstracts*, January 15, 1994.

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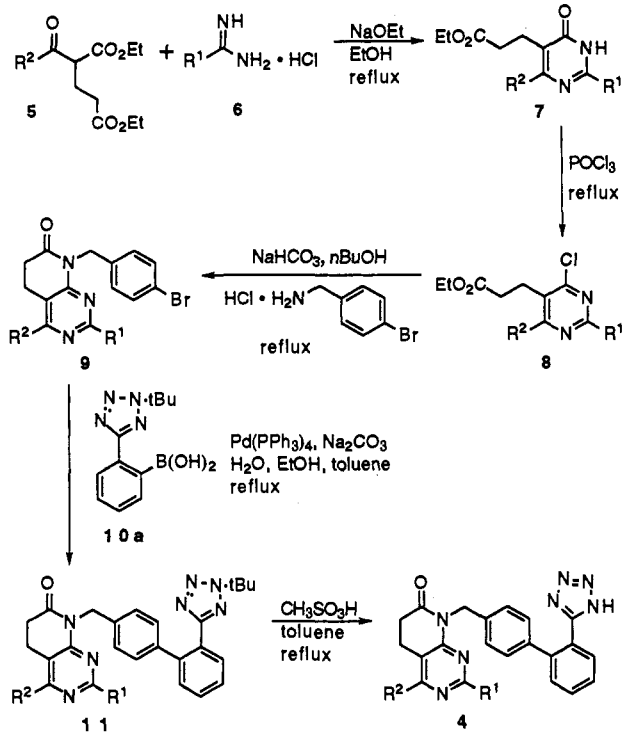
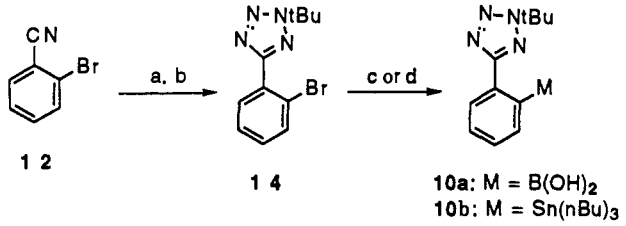
Scheme 1. Method A



Scheme 2. Method B[a]

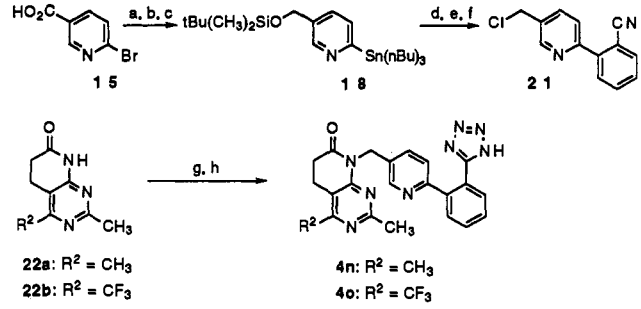


[a] (a) NaN_3, NH_4Cl, DMF, 100 °C; (b) tBuOH, H_2SO_4, CF_3CO_2H; (c) **10a**: *n*-BuLi, THF, $B(OiPr)_3$; (d) **10b**: *n*-BuLi, THF, *n*-Bu_3SnCl.

n-butyllithium and subsequent addition of triisopropyl borate[10b] gave boronic acid **10a**. Alternatively, reaction of the intermediate lithio compound with tri-*n*-butyltin chloride gave **10b**. Compound **4l** was obtained by selenium dioxide oxidation of **4a**. The hydroxymethyl group of **4k** was introduced at an earlier stage. Thus, oxidation of **9a** with selenium dioxide and reduction of the resultant aldehyde gave **9k**, which was then converted to **4k** by the remaining steps of method A. The synthesis of **4m** required the use of methoxyacetamidine because oxidation did not occur at the C-2 methyl group. The methyl protecting group of **9q** was cleaved with iodotrimethylsilane to give **9m** prior to the palladium-catalyzed coupling step.

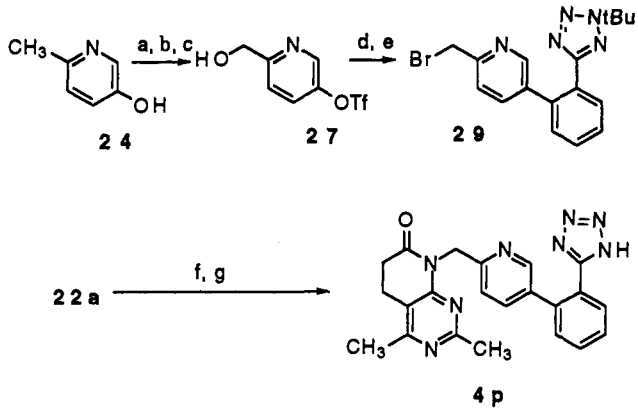
Compounds **4n–p**, which have a pyridophenyltetrazole group, were prepared according to Schemes 3 and 4. As illustrated in Scheme 3, 6-bromonicotinic acid (**15**)[12] was reduced, the resultant hydroxymethyl group was protected with a *tert*-butyldimethylsilyl group, and the stanane (**18**) was generated by sequential treatment with *n*-butyllithium and tri-*n*-butyltin chloride. Palladium-catalyzed coupling of **18** with 2-iodobenzonitrile, cleavage of the silyl group, and chlorination with thionyl chloride gave pyridophenyl nitrile **21**. Pyridopyrimidinone **22a**[13] was alkylated with nitrile **21** and the nitrile group was converted into a tetrazole with tri-*n*-butyltin azide[6a] to give **4n**. Compound **4o** was prepared similarly from **22b**.

Scheme 3



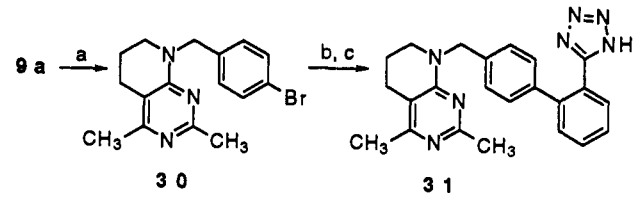
[a] (a) BH_3, THF. (b) $tBuMe_2SiCl$, Et_3N, DMF; (c) *n*-BuLi, THF, *n*-Bu_3SnCl; (d) 2-iodobenzonitrile, $(Ph_3P)_2PdCl_2$, CuI, THF, reflux; (e) *n*-Bu_4NF, THF; (f) $SOCl_2$, $ZnCl_2$, dioxane; (g) NaH, DMF, **21**; (h) NaN_3, *n*-Bu_3SnCl, xylenes, reflux.

Scheme 4



[a] (a) $(CF_3SO_2)_2O$, pyridine; (b) mCPBA, CH_2Cl_2; (c) $(CF_3CO)_2O$, reflux; (d) **10b**, $(Ph_3P)_2PdCl_2$, CuI, DMF, 100 °C; (e) Ph_3P, CBr_4, THF; (f) NaH, DMF, **29**; (g) 6 N HCl, 100 °C.

Scheme 5



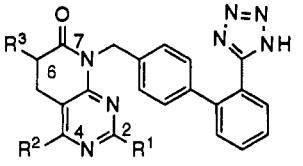
[a] (a) BH_3, THF; (b) **10a**, $(Ph_3P)_4Pd$, Na_2CO_3, H_2O, EtOH, toluene; (c) CH_3SO_3H, toluene, reflux.

The pyridine regioisomer was prepared as shown in Scheme 4. 2-Methyl-5-hydroxypyridine (**24**) was converted to a triflate (**25**) and oxidized with mCPBA to a pyridine *N*-oxide (**26**). Conversion to (hydroxymethyl)-pyridine **27** with trifluoroacetic anhydride, palladium-catalyzed coupling of **27** with stannane **10b**, and bromination with carbon tetrabromide/triphenylphosphine gave (pyridophenyl)tetrazole **29**. Alkylation of **22a** with **29** and cleavage of the *tert*-butyl group yielded compound **4p**.

The 7-desoxo analog (**31**) of **4a** was prepared by borane reduction of **9a** to give **30**, palladium-catalyzed coupling with **10a**, and cleavage of the *tert*-butyl group (Scheme 5). The 2′-carboxy analog (**32**) of **4a** was prepared by coupling **22a** with the biphenylcarboxylic acid methyl ester **33**[6a] and hydrolysis of the ester with iodotrimethylsilane (Scheme 6).

Single crystal X-ray analysis of compound **4a** revealed a torsion angle of 40° for the phenyl rings of the biphenyl group (Figure 1). The phenyl ring–tetrazole ring torsion angle is 50°. Intermolecular hydrogen bonds exist between

Table 1. Biphenyl Compounds



compd	R^1	R^2	R^3	mp, °C	formula[a]	IC_{50}, nM[b]	A II infused rat: maximum % inhibition of A II pressor response (at time, min)[c]	A II infused rat: adjusted AUC[d]
4a	CH_3	CH_3	H	198–200	$C_{23}H_{21}N_7O$	5.20	−97 ± 2 (60)	−22669
4b	CH_3	CF_3	H	219–220	$C_{23}H_{18}F_3N_7O$	24.60	−68 ± 2 (240)	−14445
4c	CH_3	CH_3	CH_3	161–163	$C_{24}H_{23}N_7O \cdot 1.25H_2O$	3.20	−63 ± 12 (30)	−11817
4d	CH_3	CH_3	di-CH_3	208–210	$C_{25}H_{25}N_7O$	3.00	−66 ± 12 (60)	−13413
4e	CH_3	Et	H	187–189	$C_{24}H_{23}N_7O$	2.30	−104 ± 4 (60)	−22259
4f	CH_3	*i*-Pr	H	190–191	$C_{25}H_{25}N_7O$	13.00	−44 ± 13 (30)	−8110
4g	CH_3	*n*-Pr	H	165–167	$C_{25}H_{25}N_7O$	1.80	−86 ± 9 (15)	−13969
4h	Et	CH_3	H	231–232	$C_{24}H_{23}N_7O$	1.30	−76 ± 31 (180)	−12986
4i	*i*-Pr	CH_3	H	193–195	$C_{25}H_{25}N_7O$	2.20	−40 ± 4 (30)	−7071
4j	*n*-Pr	CH_3	H	120–122	$C_{25}H_{25}N_7O$	1.35	−58 ± 7 (30)	−11250
4k	CH_3	CH_2OH	H	246–247	$C_{23}H_{21}N_7O_2 \cdot 0.25H_2O$	23.00	nt	nt
4l	CH_3	CHO	H	246–247	$C_{23}H_{19}N_7O_2$	50.70	nt	nt
4m	CH_2OH	CH_3	H	218–220	$C_{23}H_{21}N_7O_2$	285.0	−30 ± 12 (240)	−4641
31	7-desoxo-4a			264–266	$C_{23}H_{23}N_7$[e]	170.0	−20 ± 11 (180)	−1707
32	2′-carboxy-4a			>300	$C_{23}H_{20}KN_3O_3 \cdot 0.6H_2O$	85.0	−36 ± 6 (5)	−1228
1	losartan					34.7	−72 ± 8 (15)	−17707

[a] Satisfactory C, H, and N elemental analyses (±0.4%) were obtained, except as noted. [b] IC_{50} for inhibition of specific binding of [^{125}I]A II to rat liver membrane (n = 3). [c] Maximum percent change in A II supported mean arterial pressure at time (min) after id administration of 3 mg/kg (n = 3). [d] Adjusted area under curve. [e] C: calcd, 69.50; found, 67.43. N: calcd, 24.67; found, 24.07

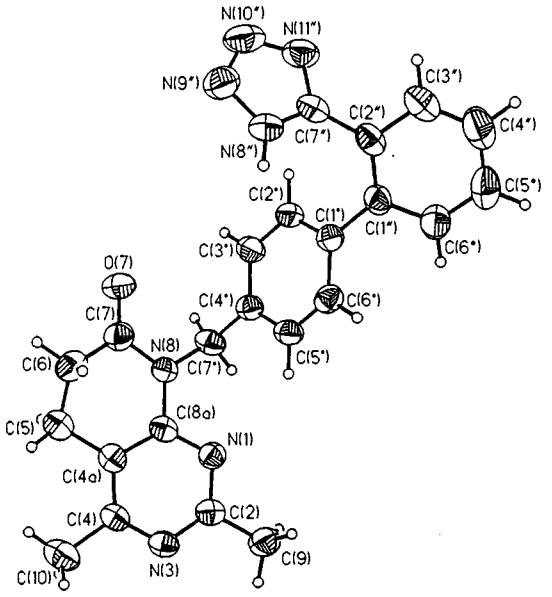


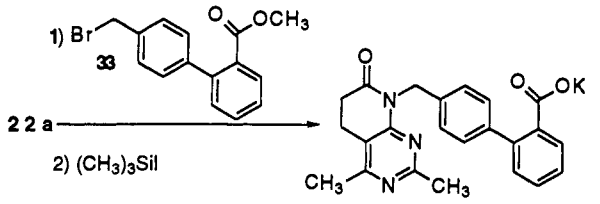
Figure 1. X-ray structure of **4a**.

the tetrazole hydrogens and the N-3 nitrogens of the pyrimidines.

In Vitro Binding. The pyridopyrimidine compounds (**4**, **31**, **32**) were tested for the inhibition of [^{125}I]A II binding in a rat liver membrane preparation (AT_1 receptors). Results are reported in Tables 1 and 2.

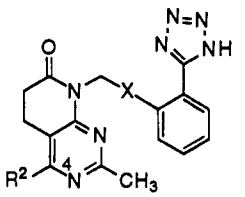
Variation of the steric bulk of the substituents on the pyridopyrimidine ring system (R^1, R^2, R^3) showed a moderate effect on in vitro binding (Table 1). The dimethyl compound (**4a**) has an IC_{50} value of 5.20 nM. Additional methyl groups (**4c** and **4d**) at position 6 (R^3) were well tolerated, lowering the IC_{50} values to 3.20 and 3.00, respectively. The introduction of larger alkyl groups at positions 2 and 4 of the ring (R^1 and R^2) was generally beneficial to binding activity. Compounds **4e** and **4g–j** were more potent than **4a**. Only the 4-isopropyl compound **4f** (IC_{50} 13.00 nM) was less potent than **4a**, suggesting that the optimal steric bulk at position 4 is exceeded by this substituent. The electronic character of the R^2 group at position 4 was also found to be important. Replacement of the 4-methyl group of **4a** with a trifluoromethyl group (**4b**) raised the IC_{50} to 24.6 nM. The introduction of a hydroxy group at position 4 (**4k**) or 2 (**4m**) lowered activity (IC_{50} 23.0 and 285 nM, respectively). Also, the 4-carbaldehyde compound **4l** was less potent (IC_{50} 50.7 nM) than **4a**. Thus, a substituent capable of participation in a hydrogen bond is not beneficial at these positions. However, a carbonyl group at position 7 is important for binding. Removal of the carbonyl group of **4a** to give the 7-desoxo compound **31** raised the IC_{50} to 170.0 nM. Thus, a hydrogen bond acceptor at position 7 appears to be important for binding to the AT_1 receptor. Replacement of the tetrazole with a carboxylic acid (**32**) led to a less potent compound, as has been observed in other series of compounds.[6a]

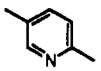
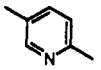
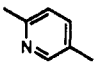
Scheme 6



The introduction of a nitrogen into the biphenyl portion (**4n–4p**, Table 2) decreased binding activity. The IC_{50} values for these compounds ranged from 24.3 to 94.9 nM. Again, hydrogen bonding or electronic effects may be responsible for this drop in activity. Also, as seen in the biphenyl series, replacement of the 4-methyl group of **4n** with a trifluoromethyl group to give **4o** further decreased potency.

Table 2. Biphenyl Substitutions



compd	R^2	X	mp, °C	formula[a]	IC_{50}, nM[b]	A II infused rat: maximum % inhibition of A II pressor response (at time, min)[c]	A II infused rat: adjusted AUC[d]
4n	CH_3		217–218	$C_{22}H_{20}N_8O$	24.3	−16 ± 3 (15)	−397
4o	CF_3		189–191	$C_{22}H_{17}F_3N_8O \cdot 0.25H_2O$	94.9	−41 ± 8 (15)	1362
4p	CH_3		208–209	$C_{22}H_{20}N_8O$	49.4	−34 ± 4 (15)	−4709

[a] Satisfactory C, H, and N elemental analyses (±0.4%) were obtained. [b] IC_{50} for inhibition of specific binding of [^{125}I]A II to rat liver membrane (n = 3). [c] Maximum percent change in A II supported mean arterial pressure at time (min) after id administration of 3 mg/kg (n = 3). [d] Adjusted area under curve.

Compounds **4a–k** and **4n** were all more potent than losartan (IC_{50} 34.7 nM) in the binding assay.

In Vivo Testing. The compounds were tested at a dose of 3 mg/kg in anesthetized, ganglion-blocked A II-infused rats for effects on blood pressure after intraduodenal (id) administration. The A II-infused rat assay demonstrates the effects of the compounds on the portion of blood pressure supported by A II. The maximum percent inhibition of the pressor response to A II and the time in minutes after dosing at which the maximum change occurred are reported for each compound (except **4k** and **4l**) in Tables 1 and 2. Also listed are the calculated areas between the MAP/time point curves for controls and tested compounds (adjusted AUC). The adjusted AUC gives a good indication of compound efficacy.

The in vivo activity of the compounds in the anesthetized rat model did not always correlate well with the in vitro binding activity. As summarized above, the addition of one or two methyl groups to position 6 of the pyridopyrimidine ring of **4a** or replacement of the 2- or 4-methyl group of **4a** with a slightly larger alkyl group resulted in a more potent compound (lower IC_{50} value). However, with the exception of compound **4e**, all of these compounds were less efficacious than **4a** in the A II infused rat model. While a trifluoromethyl group at position 4 (**4b**) decreased binding affinity by 1 order of magnitude, the effect on in vivo activity was less extreme. The low in vivo activity of compounds **4m**, **31**, and **32** is consistent with their relatively high IC_{50} values. In particular, the low activity of compound **31** which lacks a carbonyl group at position 7 again demonstrates the possible importance of a hydrogen-bond acceptor in this region of the molecule. The pyridyl analogs **4n–p** were less active than the biphenyl compounds, as expected from the relative binding affinities.

In the A II-infused rat model, losartan (1) (3 mg/kg id) caused a maximum inhibition of pressor response to A II of −72% with an adjusted AUC of −17 707. The maximum inhibition for 1 was comparable to compounds **4b–d**, **4g**, **4h**, and **4j**. However, the adjusted AUC was greater for 1 than for the above mentioned compounds, reflecting a longer duration for 1. Compound **4a** was more efficacious than 1 in the A II-infused rat model (Figure 2). The maximal response at the dose of 3 mg/kg id was greater for **4a**. Compound **4a** also appears to have longer duration than 1.

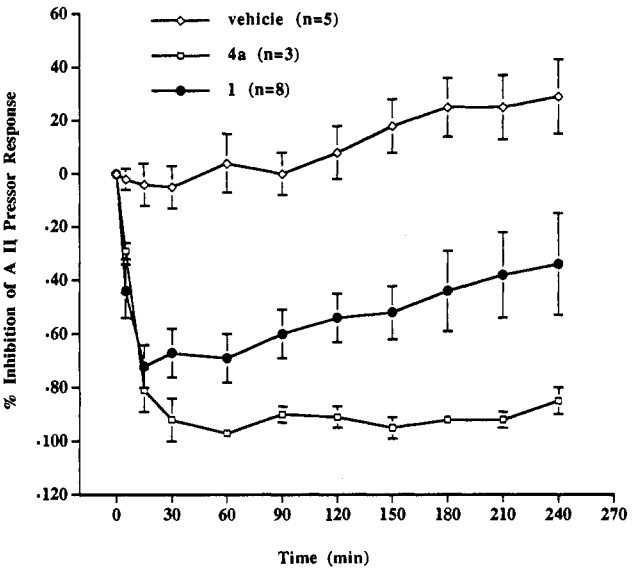


Figure 2. Effects of 1 and **4a** on pressor response to A II in anesthetized, A II-infused rats after intraduodenal administration, 3 mg/kg. Results are expressed as mean ± SE (n = 3).

The lack of correlation between binding activity and in vivo activity in the A II-infused rat for compounds **4c–j** may be due in part to lipophilicity effects seen in the in vivo model. Calculated log P (CLOGP[14]) values and measured distribution coefficients (log D; octanol/pH 7.4 phosphate buffer) for several compounds are listed in Table 3. The CLOGP for **4a** is 3.388 and the log D is 0.49. Compounds **4c** and **4e** have CLOGP values of about 3.9, but the other compounds have values of about 4.4. Thus, a CLOGP of about 3.4–3.9 seems to be necessary, but not sufficient for activity in the A II-infused rat model. Compounds **4d**, **4f**, and **4g** were less efficacious in this in vivo model and have higher CLOGP values. Compound

Table 3. Lipophilicities

compd	CLOGP[a]	log D[b]
4a	3.388	0.49 ± 0.02
4c	3.907	
4d	4.426	1.21 ± 0.07
4e	3.917	
4f	4.316	1.41 ± 0.11
4g	4.446	

[a] Calculated partition coefficient, Pomona Medchem.[14] [b] Distribution coefficient, octanol/0.01 N K_2HPO_4 (pH 7.4).

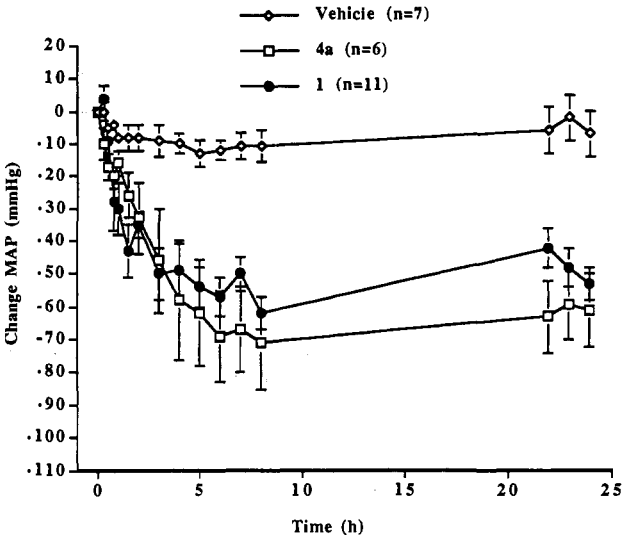


Figure 3. Effects of 1 and 4a on mean arterial pressure (MAP) in Goldblatt (2K-1C) hypertensive rats after intragastric administration. Results are expressed as mean ± SE.

4c has a CLOGP in the range of 4a and 4e but does not have comparable activity. The log D values for compounds 4a, 4d, and 4f show the same trend as the CLOGP values for these compounds.

Compound 4a was tested in Goldblatt (2K-1C) hypertensive rats. In this model the left renal artery of normotensive rats is constricted by a silver clip. The resultant hypertension is associated with an elevated plasma renin activity and increased circulating and/or tissue levels of A II. In Figure 3, the results for 4a at a dose of 1.0 mg/kg ig and 1 at a dose of 30.0 mg/kg ig are illustrated. These are the minimum doses to produce the maximum decrease in MAP (therapeutic doses). The full dose–response studies from which the therapeutic doses were determined will be reported elsewhere. The maximum decrease in MAP occurs at 8 h for both compounds and is similar in magnitude (−71 and −62 mmHg for 4a and 1, respectively). Also, both compounds have a duration of >24 h. However, compound 4a is 30 times more potent than 1 in the Goldblatt rat after oral dosing.

Summary

Described in this paper is a novel series of pyridopyrimidine compounds (4) with A II antagonist activity. Compounds with a biphenylyltetrazole pharmacophore and small alkyl groups at the 2- and 4-positions of the pyridopyrimidine ring were found to be the most potent in an AT_1 receptor binding assay and in blocking the A II pressor response in anesthetized, ganglion-blocked A II-infused rats. Compound 4a was one of the more potent compounds in the binding assay and was the most efficacious compound in the A II-infused rat model. Further study of 4a in Goldblatt (2K-1C) rats showed the compound to have oral bioavailability and to be an efficacious and potent compound in a high renin form of hypertension. Clinical evaluation of 4a is currently in progress.

Experimental Section

Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. The NMR spectra were recorded on a Varian VXR200, Varian VXR300, or a Bruker AM-400 instrument. The infrared spectra were recorded on a Perkin-Elmer diffraction grating or a Perkin-Elmer 784 spectrophotometer. The mass spectra were recorded on a Hewlett-Packard 5995A or a Finigan 8230 mass spectrometer. Analyses (C, H, N) were carried out on a modified Perkin-Elmer Model 240 CHN analyzer. Merck silica gel (70–230 mesh) was used for flash chromatography. Preparative HPLC was performed on a Waters Prep 500. Organic extracts were dried over $MgSO_4$ unless otherwise noted.

Method A. 5,8-Dihydro-2,4-dimethyl-8-[(2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl)methyl]pyrido[2,3-*d*]pyrimidin-7(6*H*)-one (4a). Step 1: Ethyl 3-(2,6-Dimethyl-4-oxo-3*H*-pyrimidin-5-yl)propionate (7a). A mixture of NaOEt (0.069 mol) in EtOH (prepared from 1.6 g of Na and 35 mL of EtOH), acetamidine hydrochloride (6a) (3.3 g, 0.035 mol), and diethyl acetylglutarate (5a) (8.0 g, 0.035 mol) was heated under reflux for 22 h. The mixture was concentrated, taken up in water, acidified to pH 4 with concentrated HCl, and extracted with EtOAc. The extracts were washed with brine, dried, and concentrated. Trituration with hexane gave 4.0 g (51%) of 7a[13] as a white solid. An analytical sample was recrystallized from ether/hexane: mp 114–116 °C; ^{1}H NMR (DMSO-d_6) δ 1.22 (t, J = 7.2 Hz, 3 H), 2.33 (s, 3 H), 2.40 (s, 3 H), 2.54 (t, J = 8.0 Hz, 2 H), 2.81 (t, J = 8.0 Hz, 2 H), 4.10 (q, J = 7.2 Hz, 2 H); IR (KBr, cm^{-1}) 1725. Anal. ($C_{11}H_{16}N_2O_3$) C, H, N.

Step 2: Ethyl 3-(4-Chloro-2,6-dimethylpyrimidin-5-yl)-propionate (8a). A mixture of 7a (3.87 g, 0.017 mol), phosphorus oxychloride (40 mL), and *N*,*N*-dimethylaniline (10 drops) was heated under reflux for 2 h. The mixture was concentrated and cooled, and ice water was added. Solid KOH was added to bring the pH to 6, and the mixture was extracted with ether. The extracts were dried and concentrated to give 2.95 g (72%) of 8a[13] as a brown oil, which solidified on standing. An analytical sample was recrystallized from hexane: mp 37–40 °C; ^{1}H NMR (DMSO-d_6) δ 1.24 (t, J = 7.2 Hz, 3 H), 2.54 (s, 3 H), 2.56 (t, J = 8.1 Hz, 2 H), 2.81 (s, 3 H), 3.04 (t, J = 8.1 Hz, 2 H), 4.14 (q, J = 7.2 Hz, 2 H). Anal. ($C_{11}H_{15}ClN_2O_2$) C, H, N.

Step 3: 5,8-Dihydro-2,4-dimethyl-8-[(4-bromophenyl)-methyl]pyrido[2,3-*d*]pyrimidin-7(6*H*)-one (9a). A mixture of 8a (8.4 g, 0.035 mol), 4-bromobenzylamine hydrochloride (8.5 g, 0.038 mol), $NaHCO_3$ (5.8 g, 0.070 mol), and *n*-BuOH (75 mL) was heated under reflux for 48 h. The mixture was diluted with EtOAc (30 mL), washed with water (100 mL), 10% aqueous HOAc (50 mL), water (100 mL), and saturated aqueous $NaHCO_3$ (2 × 100 mL), dried, and concentrated to give a yellow solid. Trituration with hexane (50 mL) gave 8.3 g (69%) of 9a as an off-white solid: mp 123–124 °C. An analytical sample was recrystallized from acetone to give a white solid: mp 124–126 °C; ^{1}H NMR (DMSO-d_6) δ 2.34 (s, 3 H), 2.42 (s, 3 H), 2.71 (t, J = 7.9 Hz, 2 H), 2.86 (t, J = 7.9 Hz, 2 H), 5.13 (s, 2 H), 7.22 (d, J = 8.3 Hz, 2 H), 7.44 (d, J = 8.3 Hz, 2 H). Anal. ($C_{16}H_{16}BrN_3O$) C, H, N.

Step 4: 5,8-Dihydro-2,4-dimethyl-8-[(2′-(2-*tert*-butyl-2*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl)methyl]pyrido[2,3-*d*]-pyrimidin-7(6*H*)-one. A mixture of 9a (2.50 g, 7.22 mmol), [2-(2-*tert*-butyl-2*H*-tetrazol-5-yl)phenyl]boronic acid (10a) (2.23 g, 7.95 mmol), 2 M Na_2CO_3 (14.5 mL, 29.00 mmol), tetrakis(triphenylphosphine)palladium(0) (250 mg, 0.219 mmol), EtOH (3 mL), and toluene (32 mL) was heated under reflux for 16 h. The mixture was concentrated, taken up in water, and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried, and concentrated to give a yellow foam. Trituration with pentane gave 2.81 g (83%) of 11a as a pale yellow solid. An analytical sample was recrystallized from ether to give an off-white solid: mp 127–130 °C; ^{1}H NMR (DMSO-d_6) δ 2.35 (s, 3 H), 2.43 (s, 3 H), 2.71 (t, J = 7.1 Hz, 2 H), 2.85 (t, J = 7.1 Hz, 2 H), 5.18 (s,

2 H), 6.97 (d, J = 8.2 Hz, 2 H), 7.18 (d, J = 8.2 Hz, 2 H), 7.44 (dd, J = 7.3, 1.3 Hz, 1 H), 7.55 (m, 2 H), 7.76 (dd, J = 7.5, 1.3 Hz, 1 H); IR (KBr, cm^{-1}) 1685. Anal. ($C_{27}H_{29}N_7O$) C, H, N.

Step 5: 5,8-Dihydro-2,4-dimethyl-8-[(2′-(1*H*-tetrazol-5-yl)-[1,1′-biphenyl]-4-yl)methyl]pyrido[2,3-*d*]pyrimidin-7(6*H*)-one (4a). A mixture of 11a (1.71 g, 3.66 mmol), methanesulfonic acid (2.40 mL, 36.6 mmol), and toluene (15 mL) was heated under reflux for 24 h. The mixture was concentrated, taken up in water, and neutralized by the addition of solid $NaHCO_3$ (3.38 g, 40.23 mmol). After 30 min of vigorous stirring, an off-white solid had formed and was collected by filtration. Trituration with ether and recrystallization from EtOH gave 1.10 g (73%) of **4a** as a white solid: mp 197–199 °C; ^1H NMR (DMSO-d_6) δ 2.35 (s, 3 H), 2.42 (s, 3 H), 2.72 (t, J = 7.2 Hz, 2 H), 2.87 (t, J = 7.2 Hz, 2 H), 5.17 (s, 2 H), 6.99 (d, J = 8.2 Hz, 2 H), 7.18 (d, J = 8.2 Hz, 2 H), 7.54 (m, 2 H), 7.65 (m, 2 H); IR (KBr, cm^{-1}) 1710. Anal. ($C_{23}H_{21}N_7O$) C, H, N.

Method B. [2-(2-*tert*-Butyl-2*H*-tetrazol-5-yl)phenyl]boronic Acid (10a). Step 1: 5-(2-Bromophenyl)-1*H*-tetrazole (13). A mixture of 2-bromobenzonitrile (12) (10.0 g, 0.055 mol), sodium azide (3.9 g, 0.060 mol), ammonium chloride (3.2 g, 0.060 mol), and DMF (90 mL) was heated at 100 °C for 18 h. The mixture was concentrated, taken up in water, and made basic (pH 9) with 1 N KOH. The aqueous mixture was extracted with ether (discarded) and acidified with 2 N HCl. The precipitate was collected by filtration to give 9.1 g (73%) of 13 as an off-white solid: mp 179–181 °C. An analytical sample was recrystallized from EtOH/toluene: mp 182–184 °C; ^1H NMR (DMSO-d_6) δ 7.56 (m, 2 H), 7.69 (dd, J = 7.0, 2.1 Hz, 1 H), 7.86 (dd, J = 7.6, 1.3 Hz, 1 H). Anal. ($C_7H_5BrN_4$) C, H, N.

Step 2: 2-*tert*-Butyl-5-(2-bromophenyl)-2*H*-tetrazole (14). To a solution of 13 (7.9 g, 0.035 mol) in trifluoroacetic acid (35 mL) was added tBuOH (5.2 g, 0.070 mol) and H_2SO_4 (1.0 mL, 0.0175 mol). After 18 h, the solution was concentrated and the residue was taken up in EtOAc. The mixture was washed with water, 2.5 N NaOH, and water, dried, and concentrated. Purification by flash chromatography (20% EtOAc/hexane) gave 6.6 g (67%) of 14 as a pale yellow oil: ^1H NMR (DMSO-d_6) δ 1.74 (s, 9 H), 7.55 (m, 2 H), 8.06 (m, 2 H). Anal. ($C_{11}H_{13}BrN_4$) C, H, N.

Step 3: [2-(2-*tert*-Butyl-2*H*-tetrazol-5-yl)phenyl]boronic Acid (10a). To a cooled (−78 °C) solution of 14 (3.35 g, 12.00 mmol) in THF (20 mL) was added 1.6 M n-BuLi in hexanes (7.80 mL, 12.50 mmol) over 2 min. The resultant yellow suspension was stirred for 30 min, and triisopropyl borate (2.35 g, 12.50 mmol) was added all at once. The cooling bath was removed, and the mixture was stirred at room temperature for 1 h. HCl (0.5 N, 20 mL) was added, and the mixture was stirred vigorously for 30 min. The layers were separated, and the aqueous phase was extracted with ether. The combined organic phases were extracted with 1 N KOH (3 × 10 mL). The aqueous extracts were acidified (pH 1) with 2 N HCl (20 mL), and the precipitate was collected by filtration to give 2.12 g (72%) of **10a** as a white solid: mp 117–122 °C; ^1H NMR (DMSO-d_6) δ 1.72 (s, 9 H), 7.46 (m, 2 H), 7.90 (m, 2 H). Anal. ($C_{11}H_{15}BN_4O_2$) C, H, N.

[2-(2-*tert*-Butyl-1*H*-tetrazol-5-yl)phenyl]tri-*n*-butylstannane (10b). To a cooled (−78 °C) solution of 14 (12.3 g, 0.043 mol) in THF (80 mL) was added 1.6 M n-BuLi in hexanes (32.7 mL, 0.052 mol). After 1 h, tri-n-butyltin chloride (17.1 g, 0.052 mol) was added, and stirring was continued for 3 h at −78 °C. The mixture was warmed to room temperature and stirred for 18 h. Water was added, and the mixture was extracted with ether. The combined extracts were washed with water and brine, dried, and concentrated to give a brown oil. Excess tri-n-butyltin chloride and remaining starting material were removed by distillation under high vacuum (1 mm) to give 9.6 g (45%) of **10b** as a brown oil: ^1H NMR (DMSO-d_6) δ 0.78 (t, J = 7.3 Hz, 9 H), 0.93 (t, J = 8.3 Hz, 6 H), 1.21 (m, 6 H), 1.43 (m, 6 H), 7.43 (d, J = 8.9 Hz, 1 H), 7.45 (d, J = 8.5 Hz, 1 H), 7.60 (dd, J = 8.9, 2.3 Hz, 1 H), 8.0 (dd, J = 8.5, 2.3 Hz, 1 H). Anal. ($C_{23}H_{40}N_4Sn$) H, N; C: calcd, 56.23; found, 56.74.

5,8-Dihydro-2,4,6-trimethyl-8-[(4-bromophenyl)methyl]pyrido[2,3-*d*]pyrimidin-7(6*H*)-one (9c). To a cooled (−78 °C) solution of **9a** (2.50 g, 7.20 mmol) in THF (25 mL) was added 2.0 M LDA (3.70 mL, 7.40 mmol). After 45 min, CH_3I (1.03 g, 7.20 mmol) was added, and the mixture was allowed to warm to room temperature over 16 h. The mixture was concentrated, and the crude product was purified by flash chromatography (60% EtOAc/hexane) to give 1.40 (54%) of **9c** as a yellow solid: mp 108–110 °C; ^1H NMR (DMSO-d_6) δ 1.14 (d, J = 6.7 Hz, 3 H), 2.36 (s, 3 H), 2.43 (s, 3 H), 2.53 (m, 1 H), 2.78 (m, 1 H), 3.05 (dd, J = 15.7, 6.2 Hz, 1 H), 5.11 (m, 2 H), 7.22 (d, J = 8.3 Hz, 2 H), 7.45 (d, J = 8.3 Hz, 2 H).

5,8-Dihydro-2,4,6,6-tetramethyl-8-[(4-bromophenyl)methyl]pyrido[2,3-*d*]pyrimidin-7(6*H*)-one (9d). To a cooled (−78 °C) solution of **9c** (1.36 g, 3.80 mmol) in THF (8 mL) was added 2.0 M LDA (2.00 mL, 4.00 mmol). After 45 min, CH_3I (0.54 g, 3.80 mmol) was added, the mixture was allowed to warm to room temperature, and stirring was continued for 64 h. The mixture was concentrated, and the crude product was purified by flash chromatography (60% EtOAc/hexane) to give 1.10 (77%) of **9d** as a yellow solid: mp 134–136 °C; ^1H NMR (DMSO-d_6) δ 1.11 (s, 6 H), 2.37 (s, 3 H), 2.44 (s, 3 H), 2.79 (s, 2 H), 5.13 (s, 2 H), 7.20 (d, J = 8.4 Hz, 2 H), 7.47 (d, J = 8.4 Hz, 2 H). Anal. ($C_{18}H_{20}BrN_3O$) C, H, N.

2-Methyl-7-oxo-8-[(2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl)methyl]-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidine-4-carbaldehyde (4l). A mixture of **4a** (822 mg, 2.00 mmol), selenium dioxide (222 mg, 2.00 mmol), and dioxane (10 mL) was heated under reflux for 6 h. Additional selenium dioxide (222 mg, 2.00 mmol) was added, and heating was continued for 18 h. The mixture was filtered, and the filtrate was concentrated. Purification by flash chromatography (10% MeOH/CH_2Cl_2) gave 316 mg of a yellow foam. The foam was triturated with acetone, and the filtrate was cooled in a freezer to give 102 mg (12%) of 4l as an off-white solid: mp 246–247 °C; ^1H NMR (DMSO-d_6) δ 2.47 (s, 3 H), 2.74 (t, J = 7.1 Hz, 2 H), 2.90 (t, J = 7.1 Hz, 2 H), 5.18 (s, 2 H), 7.00 (d, J = 8.3 Hz, 2 H), 7.20 (d, J = 8.3 Hz, 2 H), 7.54 (m, 2 H), 7.64 (m, 2 H), 8.38 (s, 1 H); IR (KBr, cm^{-1}) 1710. Anal. ($C_{23}H_{19}N_7O_2$) C, H, N.

5,8-Dihydro-2-(hydroxymethyl)-4-methyl-8-[(4-bromophenyl)methyl]pyrido[2,3-*d*]pyrimidin-7(6*H*)-one (9m). To a solution of 5,8-dihydro-2-(methoxymethyl)-4-methyl-8-[(4-bromophenyl)methyl]pyrido[2,3-*d*]pyrimidin-7(6*H*)-one (**9q**) (1.00 g, 2.70 mmol) and pyridine (0.11 g, 1.30 mmol) in $CHCl_3$ (9 mL) was added iodotrimethylsilane (0.77 g, 3.80 mmol). The mixture was heated under reflux for 30 h, and MeOH (0.5 mL) was added. The mixture was concentrated, taken up in CH_2Cl_2, washed with aqueous Na_2SO_3 and brine, dried, and concentrated. Purification by flash chromatography (5% MeOH/CH_2Cl_2) gave 0.54 g (56%) of **9m** as a colorless foam. Trituration with hexane gave a white solid: mp 134–136 °C; ^1H NMR (DMSO-d_6) δ 2.40 (s, 3 H), 2.73 (t, J = 7.6 Hz, 2 H), 2.87 (t, J = 7.6 Hz, 2 H), 4.43 (d, J = 6.2 Hz, 2 H), 5.09 (t, J = 6.2 Hz, 1 H), 5.19 (s, 2 H), 7.27 (d, J = 8.2 Hz, 2 H), 7.43 (d, J = 8.2 Hz, 2 H).

8-[(4-Bromophenyl)methyl]-2-methyl-7-oxo-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidine-4-carbaldehyde (9l). A mixture of **9a** (692 mg, 2.00 mmol), selenium dioxide (244 mg, 2.20 mmol), and dioxane (10 mL) was heated under reflux for 17 h. The mixture was filtered, and the filtrate was concentrated. Purification by flash chromatography (30% EtOAc/hexane) gave 576 mg (80%) of **9l** as a yellow solid: mp 124–126 °C; ^1H NMR ($CDCl_3$) δ 2.70 (s, 3 H), 2.73 (t, J = 7.6 Hz, 2 H), 3.37 (t, J = 7.6 Hz, 2 H), 5.27 (s, 2 H), 7.31 (d, J = 8.5 Hz, 2 H), 7.39 (d, J = 8.5 Hz, 2 H), 10.02 (s, 1 H); IR (KBr, cm^{-1}) 1710, 1695. Anal. ($C_{16}H_{14}BrN_3O_2$) C, H, N.

5,8-Dihydro-4-(hydroxymethyl)-2-methyl-8-[(4-bromophenyl)methyl]pyrido[2,3-*d*]pyrimidin-7(6*H*)-one (9k). To a solution of **9l** (550 mg, 1.53 mmol) in tetrahydrofuran (5 mL) and iPrOH (2 mL) was added sodium borohydride (116 mg, 3.05 mmol). After 45 min, the mixture was cooled to 0 °C, and CO_2 was bubbled in for 5 min. The mixture was filtered, and the filtrate was concentrated to give 677 mg of a yellow foam. Purification by flash chromatography (5% MeOH/CH_2Cl_2) gave 496 mg (90%) of product as an off-white solid: mp 159–160 °C; ^1H NMR ($CDCl_3$) δ 2.65 (s, 3 H), 2.75 (s, 4 H), 4.40 (br s, 1 H), 4.63 (s, 2 H), 5.26 (s, 2 H), 7.31 (d, J = 8.3 Hz, 2 H), 7.39 (d, J = 8.3 Hz, 2 H). Anal. ($C_{16}H_{16}BrN_3O_2$) C, H, N.

5,8-Dihydro-2,4-dimethyl-8-[[(2-(1*H*-tetrazol-5-yl)phenyl)-3-pyridin-6-yl]methyl]pyrido[2,3-*d*]pyrimidin-7(6*H*)-one (4n). Step 1: 2-Bromo-5-(hydroxymethyl)pyridine (16). To a cooled (0 °C), stirred suspension of 6-bromonicotinic acid (15)

(13.8 g, 0.068 mol), prepared according to Campbell,[12] in THF (20 mL) was added 1.0 M BH_3 in THF (204 mL, 0.204 mol). The mixture was stirred at room temperature for 3 h and recooled to 0 °C, and saturated aqueous K_2CO_3 and water were added. The mixture was extracted with EtOAc, and the combined extracts were washed with water, dried, and concentrated to give a yellow oil. Purification by flash chromatography (2% MeOH/CH_2Cl_2) gave 7.5 g (59%) of **16** as a yellow solid: mp 49–51 °C; ^{1}H NMR (DMSO-d_6) δ 4.50 (d, J = 5.7 Hz, 2 H), 5.40 (t, J = 5.7 Hz, 1 H), 7.57 (d, J = 8.3 Hz, 1 H), 7.70 (dd, J = 8.3, 1.5 Hz, 1 H), 8.35 (d, J = 1.5 Hz, 1 H).

Step 2: 2-Bromo-5-[[(*tert*-butyldimethylsilyl)oxy]methyl]pyridine (17). To a stirred mixture of **16** (4.7 g, 0.023 mol) and triethylamine (3.4 mL, 0.024 mol) in DMF (30 mL) was added *tert*-butyldimethylsilyl chloride. After 1 h, the mixture was diluted with ether and washed with water. The ether phase was dried and concentrated to give 6.8 g (97%) of **17** as a colorless oil: ^{1}H NMR (DMSO-d_6) δ 0.10 (s, 6 H), 0.90 (s, 3 H), 4.73 (s, 2 H), 7.65 (m, 2 H), 8.35 (d, J = 1.5 Hz, 1 H).

Step 3: [5-[[(*tert*-Butyldimethylsilyl)oxy]methyl]pyridin-2-yl]tri-*n*-butylstannane (18). To a cooled (−78 °C), stirred solution of **17** (6.8 g, 0.022 mol) in THF (60 mL) was added 1.6 M *n*-BuLi in hexanes (14.1 mL, 0.022 mol). After 1 h, tri-*n*-butyltin chloride (6.1 mL, 0.022 mol) was added, and stirring was continued for 3 h. Water was added, and the mixture was warmed to room temperature and extracted with ether. The combined extracts were dried and concentrated to give 11.5 g (100%) of **18** as a brown oil: ^{1}H NMR (DMSO-d_6) δ 0.10 (s, 6 H), 0.80 (m, 18 H), 1.10 (m, 6 H), 1.25 (m, 6 H), 1.50 (m, 6 H), 4.73 (s, 2 H), 7.55 (m, 2 H), 8.61 (d, J = 2.2 Hz, 1 H).

Step 4: 2-[5-[[(*tert*-Butyldimethylsilyl)oxy]methyl]pyridin-2-yl]benzonitrile (19). A mixture of **18** (11.5 g, 0.022 mol), 2-iodobenzonitrile (5.1 g, 0.022 mol), CuI (0.43 g, 0.002 mol), and bis(triphenylphosphine)palladium(II) chloride (0.80 g, 0.001 mol) in THF (40 mL) was heated under reflux for 48 h. The mixture was diluted with ether and washed with saturated aqueous NH_4Cl, aqueous NH_4OH, water, and brine, dried, and concentrated to give 4.9 g (67%) of **19** as a brown oil: ^{1}H NMR (DMSO-d_6) δ 0.10 (s, 6 H), 0.90 (s, 9 H), 4.73 (s, 2 H), 7.45 (m, 1 H), 7.60 (m, 4 H), 7.75 (dd, J = 7.9 Hz, 2.2 Hz, 1 H), 8.50 (d, J = 2.2 Hz, 1 H).

Step 5: 2-[5-(Hydroxymethyl)pyridin-2-yl]benzonitrile (20). A mixture of **19** (4.9 g, 0.021 mol) and *n*-Bu_4NF hydrate (8.1 g, 0.031 mol) in THF (60 mL) was stirred at room temperature for 18 h. The mixture was diluted with EtOAc, washed with water and brine, dried, and concentrated to give 3.5 g (80%) of **20** as a brown solid: mp 152–153 °C; ^{1}H NMR (DMSO-d_6) δ 4.61 (d, J = 5.6 Hz, 2 H), 5.42 (t, J = 5.6 Hz, 1 H), 7.57 (dd, J = 7.3, 1.5 Hz, 1 H), 7.65 (m, 4 H), 7.80 (dd, J = 7.9, 2.2 Hz, 1 H), 8.52 (d, J = 2.2 Hz, 1 H).

Step 6: 2-[5-(Chloromethyl)pyridin-2-yl]benzonitrile (21). To a cooled (0 °C), stirred solution of **20** (4.3 g, 0.020 mol) and $ZnCl_2$ (0.09 g, 0.61 mmol) in dioxane (40 mL) was added $SOCl_2$ (1.50 mL, 0.020 mol) dropwise. The mixture was stirred at room temperature for 18 h, diluted with ether, washed with water and brine, dried, and concentrated to give 4.30 g (92%) of **21** as a brown solid: mp 97–98 °C; ^{1}H NMR (DMSO-d_6) δ 4.90 (s, 2 H), 7.63 (dd, J = 7.7, 1.3 Hz, 1 H), 7.80 (m, 1 H), 7.85 (m, 2 H), 7.95 (d, J = 7.7 Hz, 1 H), 8.01 (dd, J = 8.0, 2.2 Hz, 1 H), 8.80 (d, J = 2.2 Hz, 1 H).

Step 7: 5,8-Dihydro-2,4-dimethyl-8-[[6-(2-cyanophenyl)-3-pyridinyl]methyl]pyrido[2,3-*d*]pyrimidin-7(6*H*)-one (23a). To a stirred suspension of NaH (60% dispersion in mineral oil; 0.42 g, 9.18 mmol) in DMF (20 mL) was added **22a**[13] (1.55 g, 8.75 mmol). After 1 h, **21** (2.00 g, 8.75 mmol) was added in several portions. Stirring was continued for 4 h, and the mixture was concentrated. Water was added and the mixture was extracted with CH_2Cl_2. The combined extracts were dried and concentrated to give 3.20 g (100%) of **23a** as a brown solid: mp 161–162 °C; ^{1}H NMR (DMSO-d_6) δ 2.36 (s, 3 H), 2.45 (s, 3 H), 2.78 (t, J = 7.8 Hz, 2 H), 2.87 (t, J = 7.8 Hz, 2 H), 5.27 (s, 2 H), 7.61 (m, 1 H), 7.80 (m, 4 H), 7.93 (dd, J = 7.7, 1.3 Hz, 1 H), 8.70 (d, J = 1.3 Hz, 1 H).

Step 8: 5,8-Dihydro-2,4-dimethyl-8-[[6-(2-(1*H*-tetrazol-5-yl)phenyl)-3-pyridinyl]methyl]pyrido[2,3-*d*]pyrimidin-7(6*H*)-one (4n). A mixture of **23a** (4.0 g, 10.8 mmol), NaN_3 (0.8 g, 11.9 mmol), and tri-*n*-butyltin chloride (3.9 g, 11.9 mmol) in xylenes (100 mL) was heated under reflux for 24 h. Another 1.5 equiv of NaN_3 and tri-*n*-butyltin chloride were added, and heating was continued for 24 h. The reaction mixture was concentrated, and 2 N HCl was added. The mixture was extracted with ether (discarded) and adjusted to pH 5 with 50% NaOH. The aqueous phase was extracted with CH_2Cl_2, and the extracts were washed with water, dried, and concentrated. Purification by flash chromatography (5% MeOH/CH_2Cl_2) and recrystallization from EtOH/water gave 2.8 g (63%) of **4n** as a white solid: mp 217–218 °C; ^{1}H NMR (DMSO-d_6) δ 2.35 (s, 3 H), 2.44 (s, 3 H), 2.73 (t, J = 7.8 Hz, 2 H), 2.85 (t, J = 7.8 Hz, 2 H), 5.18 (s, 2 H), 7.33 (d, J = 8.3 Hz, 1 H), 7.65 (m, 5 H), 8.36 (s, 1 H); IR (KBr, cm^{-1}) 1690. Anal. ($C_{22}H_{20}N_8O$) C, H, N.

5,8-Dihydro-2,4-dimethyl-8-[[5-(2-(1*H*-tetrazol-5-yl)phenyl)-2-pyridinyl]methyl]pyrido[2,3-*d*]pyrimidin-7(6*H*)-one (4p). Step 1: 6-Methylpyridin-3-yl trifluoromethanesulfonate (25). To a stirred, cooled (0 °C) solution of 3-hydroxy-6-methylpyridine (**24**) (14.0 g, 0.128 mol) in pyridine (70 mL) was added trifluoromethanesulfonic anhydride (39.8 g, 0.141 mol) dropwise. The mixture was stirred at room temperature for 5 h. Water was added, and the mixture was extracted with ether. The extracts were washed with brine, dried, and concentrated to give 27.3 g (88%) of **25** as a brown oil: ^{1}H NMR (DMSO-d_6) δ 2.50 (s, 3 H), 7.45 (d, J = 9.2 Hz, 1 H), 7.90 (dd, J = 9.2, 2.3 Hz, 1 H), 8.60 (d, J = 2.3 Hz, 1 H).

Step 2: 6-Methylpyridin-3-yl trifluoromethanesulfonate *N*-Oxide (26). To a stirred solution of **25** (27.3 g, 0.113 mol) in CH_2Cl_2 (140 mL) was added mCPBA (21.5 g, 0.124 mol) in several portions. After 16 h, the precipitate was removed by filtration, and the filtrate was concentrated. Purification by flash chromatography (2% MeOH/CH_2Cl_2) gave 25.0 g (86%) of **26** as colorless crystals: mp 47–48 °C; ^{1}H NMR (DMSO-d_6) δ 2.36 (s, 3 H), 7.56 (dd, J = 8.9, 2.3 Hz, 1 H), 7.69 (d, J = 8.9 Hz, 1 H), 8.84 (d, J = 2.3 Hz, 1 H).

Step 3: 6-(Hydroxymethyl)pyridin-3-yl Trifluoromethanesulfonate (27). To stirred, cooled (0 °C) **26** (25.0 g, 0.097 mol) was added trifluoroacetic anhydride (69.0 mL, 0.487 mol) dropwise. The mixture was stirred at room temperature for 30 min and then heated under reflux for 1 h. The mixture was cooled to room temperature, and 10% aqueous $NaHCO_3$ (400 mL) was added. The resultant mixture was extracted with CH_2Cl_2, and the extracts were washed with brine, dried, and concentrated. Purification by flash chromatography (2% MeOH/CH_2Cl_2) gave 10.0 g (40%) of **27** as a colorless oil: ^{1}H NMR (DMSO-d_6) δ 4.60 (s, 1 H), 5.60 (s, 1 H), 7.64 (d, J = 8.8 Hz, 1 H), 8.03 (dd, J = 8.8 Hz, 2.8 Hz, 1 H), 8.67 (d, J = 2.8 Hz, 1 H).

Step 4: 2-*tert*-Butyl-5-[2-[2-(hydroxymethyl)pyridin-5-yl]phenyl]tetrazole (28). A mixture of **27** (5.0 g, 0.019 mol), **10b** (9.5 g, 0.019 mol), bis(triphenylphosphine)palladium chloride (0.70 g, 0.97 mmol), CuI (0.37 g, 1.9 mmol), and DMF (30 mL) was heated at 100 °C for 18 h. Aqueous KF 20% was added, and the mixture was stirred at room temperature for 30 min. The precipitate was removed by filtration, and the filtrate was extracted with ether. The extracts were washed with NH_4OH, saturated aqueous NH_4Cl, water, and brine, dried, and concentrated. Purification by flash chromatography (5% EtOAc/hexane) gave 0.5 g (8%) of **28** as a yellow oil: ^{1}H NMR (DMSO-d_6) δ 1.55 (s, 9 H), 4.56 (d, J = 6.0 Hz, 2 H), 5.40 (t, J = 6.0 Hz, 1 H), 7.38 (d, J = 8.8 Hz, 1 H), 7.60 (m, 4 H), 7.90 (dd, J = 8.8, 2.3 Hz, 1 H), 8.20 (d, J = 2.3 Hz, 1 H).

Step 5: 2-*tert*-Butyl-5-[2-[2-(bromomethyl)pyridin-5-yl]phenyl]tetrazole (29). A mixture of **28** (0.50 g, 1.62 mmol), triphenylphosphine (0.51 g, 1.94 mmol), and CBr_4 (0.64 g, 1.94 mmol) in THF (30 mL) was stirred at room temperature for 16 h. The mixture was concentrated, and purification by flash chromatography (20% EtOAc/hexane) gave 0.40 g (66%) of **29** as a colorless oil: ^{1}H NMR (DMSO-d_6) δ 1.56 (s, 9 H), 4.70 (s, 2 H), 7.60 (m, 5 H), 7.95 (dd, J = 8.8, 1.6 Hz, 1 H), 8.28 (d, J = 1.6 Hz, 1 H).

Step 6: 5,8-Dihydro-2,4-dimethyl-8-[[5-(2-(1*H*-tetrazol-5-yl)phenyl)-2-pyridinyl]methyl]pyrido[2,3-*d*]pyrimidin-7(6*H*)-one (4p). To a stirred suspension of NaH (60% dispersion in mineral oil; 41 mg, 1.03 mmol) in DMF (1 mL) was added **22a**[13] (170 mg, 0.94 mmol). After 30 min, a solution of **29** (350 mg, 0.94 mmol) in DMF (5 mL) was added, and the mixture was stirred

for 3 h. The mixture was concentrated, taken up in EtOAc, and washed with water. The organic phase was dried, concentrated, and purified by flash chromatography (3% MeOH/CH_2Cl_2) to give a yellow foam. The foam was heated in 6 N HCl (2 mL) for 16 h and cooled, and the pH was adjusted to 4 with 50% NaOH. The mixture was extracted with $CHCl_3$, and the combined extracts were dried and concentrated. Trituration with EtOH/ether gave 40 mg (10%) of **4p** as a white solid: mp 208–209 °C; ^{1}H NMR (DMSO-d_6) δ 2.35 (s, 3 H), 2.37 (s, 3 H), 2.77 (t, J = 7.9 Hz, 2 H), 2.90 (t, J = 7.9 Hz, 2 H), 5.30 (s, 2 H), 7.10 (d, J = 8.8 Hz, 1 H), 7.36 (dd, J = 8.8, 1.6 Hz, 1 H), 7.60 (m, 4 H), 8.23 (d, J = 1.6 Hz, 1 H); IR (KBr, cm^{-1}) 1690. Anal. ($C_{22}H_{20}N_8O$) C, H, N.

2,4-Dimethyl-8-[(4-bromophenyl)methyl]-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidine (30). To a solution of **9a** (3.0 g, 8.7 mmol) in THF (15 mL) was added 1.0 M BH_3 in THF (10 mL, 10.0 mmol) dropwise over 10 min at room temperature. The mixture was heated under reflux for 4 h, cooled, and stirred at room temperature for 18 h. HCl (2 N, 15 mL) was added to the reaction mixture, and after 15 min the THF was removed under reduced pressure. The aqueous phase was made basic with 1 N NaOH and extracted with EtOAc. The combined extracts were dried and concentrated. Purification by flash chromatography (2% MeOH/CH_2Cl_2) gave 1.8 g (62%) of **30** as a white solid: mp 102–104 °C; ^{1}H NMR (DMSO-d_6) δ 1.81 (m, 2 H), 2.07 (s, 3 H), 2.13 (s, 3 H), 2.57 (t, J = 6.2 Hz, 2 H), 3.15 (t, J = 5.5 Hz, 2 H), 4.80 (s, 2 H), 7.20 (d, J = 8.2 Hz, 2 H), 7.52 (d, J = 8.2 Hz, 2 H).

4'-[(2,4-Dimethyl-7-oxo-6,7-dihydro-5*H*-pyrido[2,3-*d*]pyrimidin-8-yl)methyl]biphenyl-2-carboxylic Acid Potassium Salt (32). To a solution of **22a**[13] (500 mg, 2.82 mmol) in DMF (5 mL) was added NaH (60% dispersion in mineral oil; 124 mg, 3.10 mmol) at room temperature. After 30 min, **33**[6a] (80% pure; 1.08 g, 2.82 mmol) was added. The mixture was stirred for 2.5 days, diluted with EtOAc, and washed with brine, and the organic phase was dried and concentrated. Purification by flash chromatography (1% MeOH/CH_2Cl_2) gave 800 mg (71%) of methyl 4'-[(2,4-dimethyl-7-oxo-6,7-dihydro-5*H*-pyrido[2,3-*d*]pyrimidin-8-yl)methyl]biphenyl-2-carboxylate (**34**) as a brown foam: ^{1}H NMR ($CDCl_3$) δ 2.42 (s, 3 H), 2.59 (s, 3 H), 2.75 (m, 2 H), 2.85 (m, 2 H), 3.60 (s, 3 H), 5.35 (s, 2 H), 7.20 (d, J = 8.2 Hz, 2 H), 7.32 (m, 1 H), 7.37 (dd, J = 7.6, 1.3 Hz, 1 H), 7.44 (d, J = 8.2 Hz, 2 H), 7.46 (m, 1 H), 7.77 (dd, J = 7.6, 1.0 Hz, 1 H).

A solution of **34** (800 mg, 1.99 mmol) and iodotrimethylsilane (797 mg, 3.98 mmol) in CH_2Cl_2 (20 mL) was heated under reflux for 22 h. Additional iodotrimethylsilane (797 mg, 3.98 mmol) was added, and heating was continued for 20 h. Saturated aqueous $NaHCO_3$ and EtOAc were added, and the layers were separated. The organic phase was extracted with saturated aqueous $NaHCO_3$, and the combined aqueous layers were treated with $Na_2S_2O_3$, extracted with CH_2Cl_2 (discarded), and acidified to pH 4 with concentrated HCl. The mixture was extracted with CH_2Cl_2, and the combined extracts were dried and concentrated to give 400 mg of an off-white solid. Recrystallization from EtOH gave 316 mg (41%) of **32** (acid) as a white solid: mp 215–216 °C. Anal. ($C_{23}H_{21}N_3O_3$) C, H, N.

Compound **32** (acid) was converted to a potassium salt as follows: a mixture of **32** (acid) (300 mg, 0.774 mmol) and 1 N KOH (736 μL) was stirred for 10 min. The mixture was filtered, and the filtrate was concentrated to give 310 mg (99%) of **32** as an off-white solid: mp >300 °C; ^{1}H NMR (DMSO-d_6) δ 2.36 (s, 3 H), 2.48 (s, 3 H), 2.73 (m, 2 H), 2.89 (m, 2 H), 5.22 (s, 2 H), 7.12 (m, 3 H), 7.20 (m, 3 H), 7.39 (dd, J = 6.6, 1.7 Hz, 2 H); IR (KBr, cm^{-1}) 1680. Anal. ($C_{23}H_{20}KN_3O_3 \cdot 0.6H_2O$) C, H, N.

Single-Crystal X-ray Analysis of 4a. A suitably cut fragment roughly 0.12 × 0.18 × 0.25 mm in size was isolated from a batch of clustered colorless plates and prisms (from EtOH), mounted on a glass fiber with epoxy cement, and then transferred to a Siemens P4 four-circle diffractometer for characterization and data collection. Intensity data were obtained with graphite monochromated Mo Kα (λ = 0.710 73 Å) radiation. The unit cell parameters for the sample were determined from the angular settings of 25 well-centered reflections ($20 \le 2\theta \le 34°$) and were as follows: a = 16.522(3), b = 7.784(1), c = 17.091(2) Å; β = 109.56(2)°; and V = 2017.1(5) Å^3. A limited search through an octant of reciprocal space revealed reflection conditions corresponding to $h01$, $h + l = 2n$, $h00$, $h = 2n$, $0k0$, $k = 2n$ and $00l$, $l = 2n$, indicating that the compound had crystallized in the monoclinic space group $P2_1/n$.

One quadrant of data ($+h,+k,\pm l$) was collected in the ω scan mode with 2θ ranging from 4.0 to 50.0°, and scan speeds varying from 3.97 to 8.08 deg/min. Three standards were measured for every 97 reflections during the data collection period, and showed no significant deviations from their mean intensity values (0.9858, 0.9989, 1.0106 for minimum, mean, maximum, respectively, i.e., < 2% variation and random). A total of 4108 reflections were measured and corrected for Lorentz and polarization effects, but not for absorption or extinction. Of these, 3664 were unique and 1894 reflections had $F > 3.0\sigma(F)$ and were considered observed.

The structure was successfully solved by direct methods (XS: TREF) in the monoclinic space group $P2_1/n$ (No. 14) and refined by full-matrix least-squares.[15] All of the non-hydrogen atoms were refined with anisotropic displacement coefficients, hydrogen atoms were allowed to ride on their respective carbons [C–H = 0.96 Å, U(H) = 1.2U(C)], and a weighting scheme based on $\sigma(F)$ was employed. The N-bound H (8″) atom was located in a difference-Fourier map, and its positional parameters were free to vary in subsequent cycles of least-squares [U(H) = 1.2U(N)]. The final residuals were $R(F)$ = 6.97% and $R_w(F)$ = 6.44% with a value of 1.33 for the goodness of fit.[16]

The empirical formula for **4a** is $C_{23}H_{21}N_7O$, the formula weight 411.5, Z = 4, and the calculated density is 1.320 mg/m^3.

Pharmacology: [^{125}I]A II Binding Assay. Rat liver membrane was obtained as a kit from New England Nuclear (NED-014A, Boston, MA). The membrane was diluted and the A II reconstituted with the diluent buffer provided with the kit. The final concentrations of A II were 10^{-10}–10^{-7} M for the standard and 10^{-4} M for determination of the nonspecific binding. The [^{125}I]A II was diluted in deionized water. The test compounds were dissolved in 50% DMSO as concentrates. For the assay, 25 μL of a standard, reference, test compound or vehicle was pipetted into appropriate test tubes. In addition, 25 μL of diluted [^{125}I]A II and 200 μL of membrane suspension were pipetted into each test tube. The contents of the test tube were mixed and incubated for 3 h at room temperature. The incubation was stopped by addition of saline and filtration onto a glass fiber filter. The filter disks were counted in a γ counter to determine the [^{125}I]A II binding to the rat liver membrane. The IC_{50} values were determined as the concentration of the compound required to inhibit the specific [^{125}I]A II binding by 50% of the vehicle control.

Anesthetized, Ganglion-Blocked A II-Infused Rats. Male Sprague–Dawley rats, weighing 300–400 g and fasted overnight, were anesthetized with Dial-Urethane and surgically prepared. The trachea was cannulated with PE240 tubing, and the left femoral artery and vein were cannulated with PE50 tubing. Two cannulas were placed in the femoral vein. A small midline abdominal incision was made, and the initial portion of the duodenum was exposed. A length of PE50 tubing was then inserted so that direct intraduodenal injections of test compounds could be made. The initial arterial pressure and heart rate were measured for 10–15 min, followed by an intravenous administration of mecamylamine at 3 mg/kg to block the ganglion. Mecamylamine was given every 90 min throughout the remainder of the experiment. The ganglion blockade caused a fall in arterial pressure of about 50 mmHg. An A II infusion was then begun into the other venous cannula at 0.25 μg/kg/min and the arterial pressure returned to or slightly above the control level. Once arterial pressure had stabilized with the A II infusion, baseline values for mean arterial pressure (MAP) were taken. The test compound, suspended in methyl cellulose, was then administered via the duodenal cannula in a volume of 1 mL/kg. Mean arterial pressure values were measured for 240 min after administration of the test compound. The fall in arterial pressure following the administration of the test compound is expressed as a percent of the portion of A II supported arterial pressure.

Goldblatt (2K-1C) Hypertensive Rats. Sprague–Dawley rats weighing 150 g were anesthetized with pentobarbital (50 mg/kg ip), and the left renal artery was clipped with a silver wire bent to an internal diameter of 0.2 mm. The hypertension was established 4–7 weeks after clipping. At that time, the animals were anesthetized with pentobarbital (50 mg/kg ip), and the right carotid artery was cannulated. The catheter was passed sub-

cutaneously to the dorsal side of the neck and exteriorized. The animals were fasted overnight but allowed access to water, and the experiment was performed the next morning. The carotid catheter was connected to a blood pressure transducer which was linked to a MI² computer data acquisition system or to a Grass or Beckman recorder for the recording of mean arterial pressure (MAP) and heart rate. The rats were given either compound **4a** (1.0 mg/kg), losartan (1) (30 mg/kg), or vehicle (0.5% methyl cellulose in distilled water) by gastric gavage in a volume of 5 mL/kg. In the experiments with **4a** and 1, saline was infused into the arterial cannula at 5 μL/min throughout the experiment to maintain patency of the cannula. A separate vehicle control group was run with a saline infusion into the arterial cannula. Each compound was administered to a separate group of 6–12 rats and MAP, and heart rates were recorded for 24 h. Data was recorded every 15 min for the first hour, every 30 min for the second hour, hourly up to 8 h, and then at 22, 23, and 24 h following dosing. At each time point following dosing, averages were determined for absolute MAP, change in MAP (in mmHg), and heart rate for all animals, and the standard error of the mean was calculated.

Acknowledgment. We express our appreciation to the Analytical Department of Wyeth-Ayerst for elemental analyses and spectral data.

Supplementary Material Available: A listing of atomic coordinates, bond lengths and angles, isotropic and anisotropic thermal parameters, and H atom coordinates for compound **4a** (5 pages). Ordering information is given on any current masthead page.

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(16) (a) $R(F) = \Sigma \| F_o| - |F_c| | / \Sigma |F_o|$. (b) $R_w(F) = [\Sigma w(|F_o| - |F_c|)^2 / \Sigma w |F_o|^2]^{1/2}$. (c) $S = [\Sigma w(|F_o| - |F_c|)^2 / (M - N)]^{1/2}$ where M is the number of observed reflections and N is the number of parameters refined.