4-(Heteroarylthio)-2-biphenylyltetrazoles as Nonpeptide Angiotensin II Antagonists

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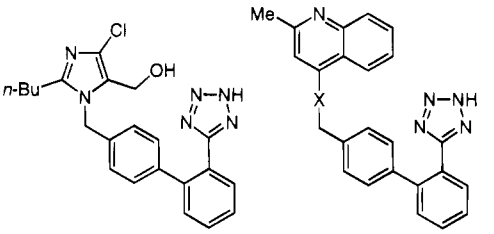
A series of 4-(heteroarylthio)-2-biphenylyltetrazoles was prepared, and the compounds were examined for their ability to displace [^{3}H]AII from angiotensin II receptors. Analogues that exhibited significant receptor binding affinities at less than 10 μM were investigated further for potential antagonism of angiotensin II-mediated contraction of rabbit isolated aortic rings. Three 4-(heteroarylthio)-2-biphenylyltetrazoles were identified that exhibited sub-micromolar angiotensin II receptor binding affinities. These compounds and two reference agents, saralasin and losartan (DUP-753), exhibited concentration-dependent reversal of angiotensin II contraction in isolated aortic rings parallel to their receptor binding affinities. Molecular modeling studies were conducted to examine the conformational effects of the novel sulfide bridging unit contained in these 4-(heteroarylthio)-2-biphenylyltetrazoles. The biological effects of the sulfide bridge as well as alterations in the heteroaromatic moiety were investigated, and the resulting structure–activity relationships are discussed.

Introduction

During the past several years, investigators interested in the development of new therapies for cardiovascular diseases have focused on the renin–angiotensin system.[1–3] These therapies have sought to regulate the effect of angiotensin II, a hormone with diverse metabolic effects including potent vasoconstriction. With an increased understanding of the dynamics of the renin–angiotensin system, researchers have been able to successfully inhibit the renin–angiotensin cascade at various stages. For example, a series of renin inhibitors have been developed that inhibit the cleavage of angiotensinogen to angiotensin I, the precursor to angiotensin II, which is the physiologically active component of the renin–angiotensin system.[5–7] Angiotensin-converting enzyme (ACE) inhibitors, such as enalapril and captopril, effectively block the next step in the cascade, the conversion of angiotensin I to angiotensin II.[4,8–10] Another approach to blocking the renin–angiotensin and the effect of angiotensin II would be by the use of selective angiotensin II receptor antagonists. By avoiding the bradykinin-potentiating action of ACE inhibitors, angiotensin II antagonists may have a better therapeutic profile. Initial research in this area led to the development of saralasin, an octapeptide that lowers blood pressure by displacing endogenous angiotensin II from its vascular receptor.[11–13] However, it was the discovery of nonpeptide angiotensin II antagonists that initiated an explosion of activity in this field. For example, Duncia, Carini, and co-workers conducted elegant structure–activity investigations that led to the development of losartan (**1**, DUP-753), a potent and selective angiotensin II antagonist useful for the treatment of hypertension.[14–16]

Since the discovery of these potent nonpeptide angiotensin II antagonists, the structure–activity relationships (SARs) of this class of compounds have been extensively studied. Initially, the major structural modifications were made to the heterocyclic group while maintaining the biphenylyltetrazole moiety. For example, pyrimidines,[17] triazoles,[18] imidazo[4,5-*b*]pyrimidines,[19] benzimidazoles,[20] quinolines,[21,22] pyrazoles,[23] dihydropyrimidines,[24] and imidazolones [25] have been used to replace the imidazole head group of losartan. In most cases, the biphenylyltetrazole moiety has been attached to the heterocycle by a bridging methylene group. However, in the 2-alkylquinoline series reported by Bradbury *et al.*, the groups were linked with a methyleneoxy, a methylenethio, or an ethylene bridge (e.g., **2**, **3**, and **4**, respectively).[21,22] From these reports, it was interesting to note that activity could be maintained with a longer bridging unit (methyleneoxy vs methylene). Through extensive molecular mechanics calculations, Bradbury showed that certain low-energy conformations of an imidazole–methylene–biphenyl (e.g., **1**) and the quinoline–methyleneoxy–biphenyl (e.g., **2**) antagonists had good correspondence between the tetrazole groups and the N-1 atoms of the quinoline and imidazole rings. We postulated that a shorter linking bridge between the quinoline heterocycle and the biphenylyltetrazole group in this class of compounds might allow for a better overlap of the putative pharmacophores (hydrogen-bond acceptor in the heterocycle and the tetrazole NH) with those found in losartan. A sulfide bridge was chosen as the alternative linking unit for this investigation. We envisaged that sulfides of this type could be obtained by alkylation of an appropriately



1; (DUP-753, losartan)

2; X = O (ICI-D8731)
3; X = S
4; X = CH_2

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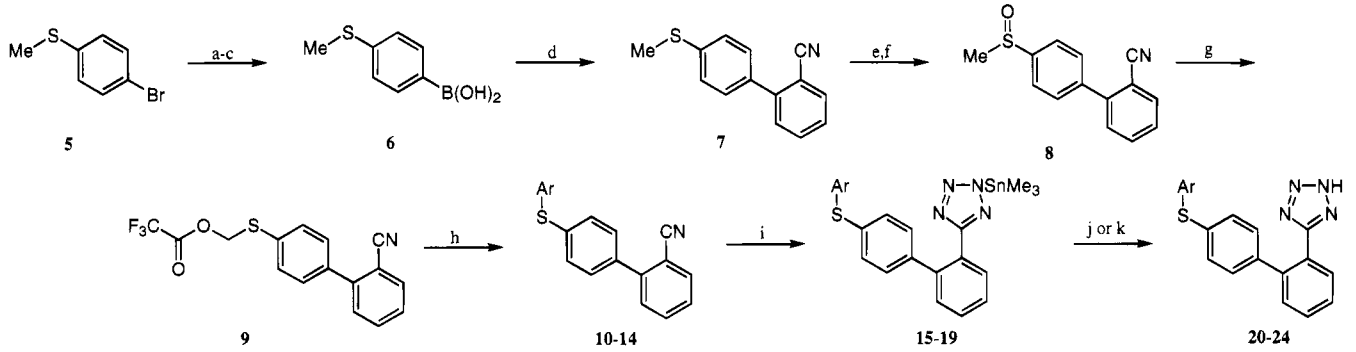
Scheme 1[a]



[a] Reagents: (a) *n*-BuLi, THF; (b) B(O-*i*-Pr)$_3$, −78 °C to room temperature; (c) H_2O, HCl; (d) 2-bromobenzonitrile, $(P(Ph)_3)_4Pd$, 2 M Na_2CO_3, EtOH, toluene, reflux; (e) *m*-CPBA, CH_2Cl_2, -78 °C; (f) aqueous $Ca(OH)_2$; (g) $(CF_3CO)_2O$, reflux; (h) ArCl, MeOH, NEt_3, reflux; (i) N_3SnMe_3, toluene, reflux; (j) HCl, MeOH; (k) silica gel, CH_2Cl_2/MeOH (9:1).

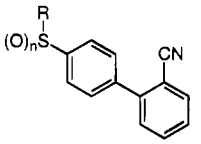
substituted 4-thiobiphenyl compound with a heteroaryl halide. This approach not only provided the analogue necessary to investigate the effect of the sulfide bridge but also allowed for the preparation of several derivatives with alternative heterocyclic replacements. In this paper, we report the synthesis and biological evaluation of a series of potential angiotensin II antagonists containing a 4-thiobiphenylyltetrazole subunit.

Chemistry

The general synthetic route employed to prepare sulfides **20**−**24** is outlined in Scheme 1. To obtain the targeted sulfides, a 4-thiobiphenyl nucleophile was required to react with a variety of heteroaryl halides. Formation of such an arylthio compound was problematic owing to oxidation of the free thiol to the corresponding disulfide. Therefore, it was necessary to employ an arylthio protecting group that would be stable to biphenyl formation and would provide the thiol anion upon deprotection. This anion could then be reacted directly with the heteroaromatic electrophile *in situ* to avoid disulfide formation. A methyl protecting group fulfilled these requirements.

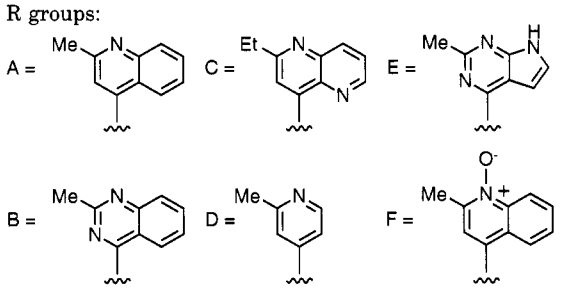
Commercially available 4-bromothioanisole (**5**) underwent halogen−metal exchange with *n*-butyllithium in tetrahydrofuran. The resulting anion was treated with triisopropyl borate, giving an intermediate borate that was quenched with aqueous hydrochloric acid to give boronic acid **6** in 82% yield. Palladium-catalyzed cross-coupling reaction of boronic acid **6** with 2-bromobenzonitrile by the method developed by Suzuki *et al.* provided 2-(4-(methylthio)phenyl)benzonitrile (**7**).[26] Sulfoxide **8** was obtained by oxidation of sulfide **7** with *m*-chloroperoxybenzoic acid (*m*-CPBA) in dichloromethane at −78 °C. Conducting or quenching the reaction at higher temperatures increased formation of the undesired sulfone. Conversion of sulfoxide **8** into the required arylthio nucleophile was accomplished by the deprotection sequence described by Young and coworkers, as follows.[27] Pummerer rearrangement of 4′-(methylsulfinyl)-2-biphenylcarbonitrile (**8**) by treatment with refluxing trifluoroacetic anhydride provided hemithioacetal acetate **9**. This intermediate was immediately hydrolyzed with methanol in the presence of an appropriate heteroaryl chloride. As the free aryl thiol anion was liberated, it reacted with an appropriate electrophile *in situ* to generate 4-(thio-substituted)-2-biphenylcarbonitriles **10**−**14**. The physical properties of these intermediate nitriles are reported in Table 1.

Table 1. Characterization Data for 4-(Heteroarylthio)-2-biphenylcarbonitrile Intermediates



compd no.	R[a]	*n*	yield, %	mp, °C	formula	anal.[b]
7	Me	0	63[c]	84−84.5	$C_{14}H_{11}NS$	C, H, N, S
8	Me	1	83[c]	114−115	$C_{14}H_{11}NOS$	C, H, N, S
10	A	0	70[f]	154.5−155.5	$C_{23}H_{26}N_2S$	C, H, N
11	B	0	73[d]	173−174	$C_{22}H_{15}N_3S$	C, H, N, S
12	C	0	38[e]	133−134	$C_{23}H_{17}N_3S$	C, H, N, S
13	D	0	41[f]	142−144	$C_{19}H_{14}N_2S$	C, H, N, S
14	E	0	34[g]	240−241	$C_{20}H_{14}N_4S$	C, H, N
25	F	2	11[c]	212 dec	$C_{23}H_{16}N_2O_3S \cdot 0.5H_2O$	C, H, N, S

[a] R groups:

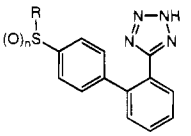


[b] All combustion analyses were within ±0.4% of the theoretical values. [c] Purified by chromatography on silica gel with mixtures of hexane/ethyl acetate as eluant. [d] Triturated with hot isooctane and recrystallized from hexanes/CH_2Cl_2. [e] Recrystallized from isooctane. [f] Recrystallized from an isooctane/CH_2Cl_2 mixture. [g] Purified by flash chromatography on silica gel with mixtures of methanol/CH_2Cl_2 as eluant.

Treatment of nitriles **10**−**14** with trimethyltin azide[28] provided tin tetrazole intermediates **15**−**19**. Hydrolysis of these intermediates was accomplished on silica gel or by treatment with methanolic hydrochloric acid to give the target tetrazoles **20**−**24**. When methanolic hydrochloric acid was used, the products were obtained as hydrochloride salts.

One of the most potent compounds in this series was quinoline derivative **20** (*vide supra*). To extend our SAR study, we wanted to investigate how the oxidation of this derivative would effect *in vitro* receptor binding. The synthesis of the sulfone/*N*-oxide (**28**) of quinoline **20** is outlined in Scheme 2. The initial approach to obtain this derivative involved oxidation of nitrile **10** with *m*-CPBA to give compound **25**. However, a poor

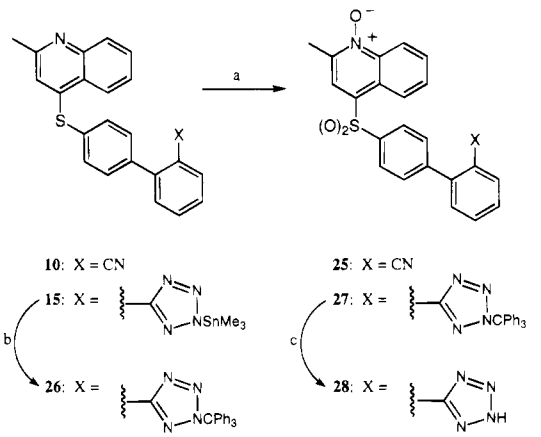
Table 2. Characterization and *in Vitro* Angiotensin II Receptor Binding Affinities for 4-(Heteroarylthio)biphenylyltetrazoles **20-24**, **26**, and **28**



compd no.	R[a]	n	yield, %	mp, °C	formula	anal.[b]	angiotensin II receptor binding IC_{50}, μM[c]
20	A	0	70[d]	180 dec	$C_{23}H_{17}N_5S \cdot HCl \cdot 0.9H_2O$	C, H, N, S, H_2O	0.096
21	B	0	26[e]	199.5–201	$C_{22}H_{16}N_6S \cdot 0.25HCl$	C, H, N	0.35
22	C	0	42[f]	206 dec	$C_{23}H_{18}N_6S \cdot HCl \cdot 0.5H_2O$	C, H, N, S, Cl	0.020
23	D	0	53[g]	121–124	$C_{19}H_{15}N_5S \cdot 0.75HCl \cdot 0.25H_2O$	C, H, N, Cl	1.5
24	E	0	7[h]	226–228	$C_{20}H_{15}N_7S \cdot 0.2HCl$	C, H, N	>10
28	F	2	25[g]	167 dec	$C_{23}H_{17}N_5O_3S$	C, H, N	>10
26[i]	A	0	68[j]	182–183	$C_{42}H_{31}N_5S$	C, H, N	4.7
1, DUP-753 (losartan)							0.0046
2, ICI-D8731							0.031[k]
3, SCH_2 derivative							0.37[k]
4, CH_2CH_2 derivative							0.27[k]

[a] See Table 1 for R group designations. [b] All combustion analyses were within ±0.4% of the theoretical values. [c] Inhibition of [^{3}H]angiotensin II binding. [d] Precipitated from MeOH. [e] Triturated with MeOH/CH_2Cl_2. [f] Recrystallized from MeOH/EtOAc. [g] Precipitated from Et_2O/CH_2Cl_2. [h] Recrystallized from EtOH/H_2O. [i] Trityl-protected tetrazole (see Scheme 2). [j] Recrystallized from isooctane/CH_2Cl_2. [k] Reference 22; inhibition of [^{125}I]angiotensin II binding.

Scheme 2[a]



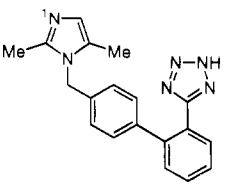
[a] Reagents: (a) *m*-CPBA, CH_2Cl_2, -78 °C to room temperature; (b) Ph_3CCl, NaOH, CH_2Cl_2/THF; (c) HCl, Et_2O, CH_2Cl_2.

yield was obtained in this reaction, resulting in insufficient quantities of nitrile **25** to proceed to the desired tetrazole. An alternative route involving a protected tetrazole intermediate proved to be more successful. Treatment of tin tetrazole **15** with trityl chloride and sodium hydroxide provided the trityl-protected tetrazole **26**. The sulfoxide/*N*-oxide **28** was obtained by the oxidation of **26** with *m*-CPBA, followed by deprotection of the resulting trityl tetrazole **27** with hydrochloric acid. The physical properties of tetrazoles **20–24**, **26**, and **28** are summarized in Table 2.

Results and Discussion

As a primary screen, tetrazoles **20–24**, **26**, and **28** were assayed *in vitro* for their ability to displace [^{3}H]-AII from the angiotensin II receptor isolated from the liver of Sprague–Dawley rats.[29,30] These results are expressed as IC_{50}'s and are reported in Table 2. Receptor binding affinities for standard compounds **1–4** are also included for comparison.

A 4-fold increase in receptor binding affinity was obtained with a sulfide bridge connecting the quinoline heterocycle to the biphenyl moiety (compound **20**) as compared to a methylenethio linking unit (compound **3**). This result suggested that the shorter distance from the nitrogen of the quinoline to the tetrazole pharmacophore was beneficial to *in vitro* binding affinity. However, compound **20** was slightly less active than the corresponding methyleneoxy derivative **2**. These results prompted us to examine the relative conformational and structural differences between the sulfide-, methyleneoxy-, and methylene-bridged compounds. Since losartan (**1**) has been the standard to which all new angiotensin II antagonists have been compared, we wanted to conduct superimposition studies of quinolines **2** and **20** with a biphenyl imidazole such as **1**. Rather than using the complete structure of **1**, dimethylimidazole **29** was employed in these superimposition studies, since Bradbury *et al.* previously reported the systematic development of a low-energy conformation of **29** as a suitable model for **1**.[22] The coordinates of dimethylimidazole **29** and ICI-D8731 (quinoline **2**) reported by Bradbury were used as a starting point for our investigation.[22] The conformation of sulfide **20** was obtained using the coordinates of compound **2** as a template. The protonated forms of the heterocycles were used in each superimposition study. Three different superimposition methods were employed: atom-based rigid superimpositions, atom-based flexible superimpositions, and superimpositions using electrostatic field potentials.



29

The first approach overlaid the biphenyl subunits, which were common to all of the derivatives, using the rigid superimposition algorithm in MacroModel.[31] The results are illustrated in Figure 1. For each superimposed pair, the distances between the N-1 nitrogen of the imidazole and the quinoline were measured, and the

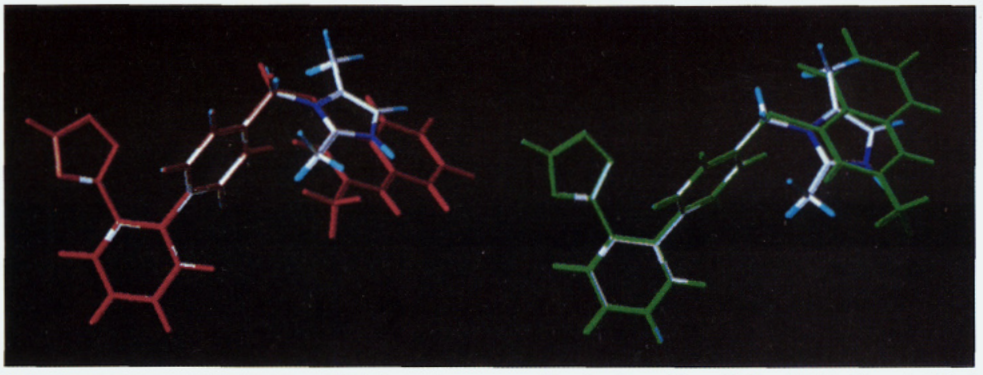


Figure 1. Rigid superimpositions of the biphenylyltetrazole groups of quinolines **2** and **20** with imidazole **29.** (a, left) **2** (red) and **29** (colored by atom type). (b, right) **20** (green) and **29** (colored by atom type).

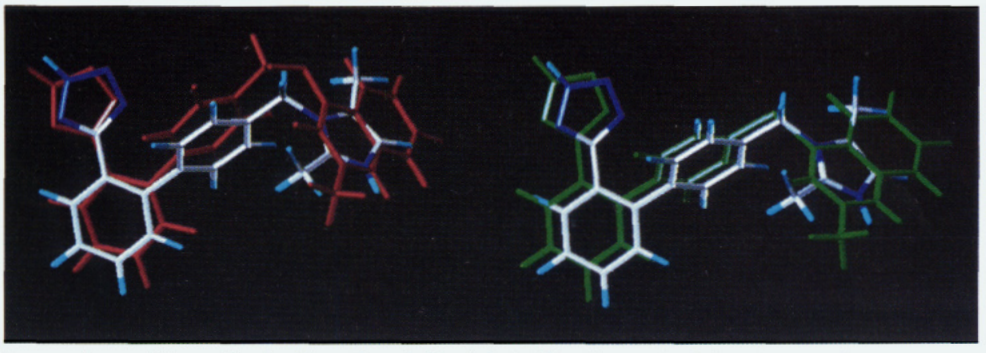


Figure 2. Flexible superimpositions of quinolines **2** and **20** with imidazole **29.** (a, left) **2** (red) and **29** (colored by atom type). (b, right) **20** (green) and **29** (colored by atom type).

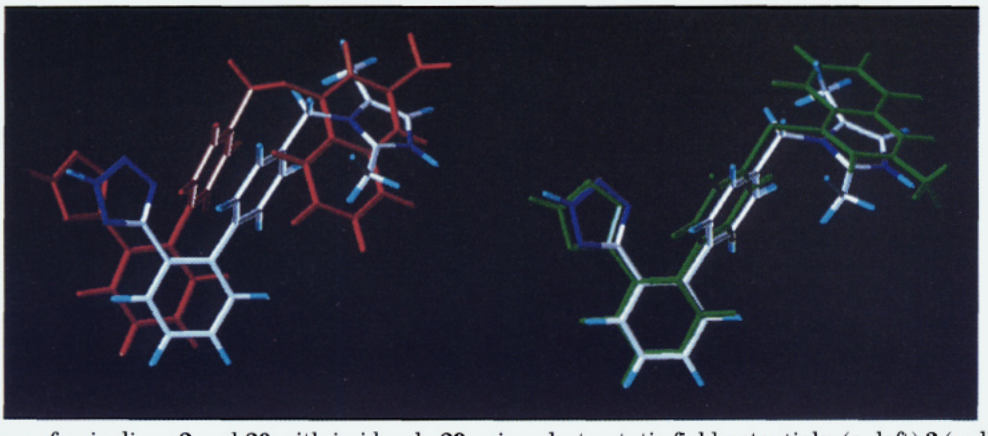


Figure 3. Overlays of quinolines **2** and **20** with imidazole **29** using electrostatic field potentials. (a, left) **2** (red) and **29** (colored by atom type). (b, right) **20** (green) and **29** (colored by atom type).

directions of the corresponding N−H vectors were compared. The N-1 nitrogen of quinoline **20** corresponded more closely to the N-1 nitrogen of imidazole **29** (1.3 Å for **20** vs **29**; vs 2.1 Å for **2** vs **29**); however, the N−H bond vectors of quinoline **2** and imidazole **29** were more comparable (Figure 1a vs Figure 1b). If the direction of the N−H bond is an important factor, the increased flexibility of compound **2** may allow for a more favorable interaction at the receptor site.

In the second approach, the protonated nitrogen of the tetrazole, the ipso-aromatic carbons, and the N−H groups of the imidazole and quinolines were selected for superimposition, and the flexible bonds were allowed to rotate using the flexible superimposition algorithm in MacroModel.[31] The results of the flexible superimpositions are illustrated in Figure 2. In this case, the N-1 nitrogen of compound **2** shows a better overlap with the N-1 of the imidazole than was observed for compound **20**. The local fit favors compound **2**, as indicated by the corresponding RMS values (RMS = 0.53 for **2** vs **29**; vs 0.64 for **20** vs **29**). However, a compromise in the fit can be seen in the puckering of the methyleneoxy bridge of **2** (Figure 2a), while the biphenyl subunit for compound **20** is in good alignment (Figure 2b).

The final method that was examined employed electrostatic field potentials. A Monte Carlo search was conducted to find the optimum field fit between the two molecules using the field fit tools in Sybyl version 6.[32] These results are illustrated in Figure 3. Employing this method of analysis, the backbone of sulfide **20** showed a much closer correspondence with imidazole **29** than did quinoline **2** (Figure 3b vs Figure 3a). The difference in energy of the two electrostatic field superimpositions also confirmed this visual observation (E = 5123 kcal for **2** vs 4671 kcal for **20**).[33]

These molecular modeling experiments indicated that the shorter thio-bridged compound (quinoline **20**) has an overlap with the losartan model compound **29** that

is comparable to, or in some cases better than, that of ICI-D8731 (**2**). The differences discussed above for the methyleneoxy derivative would be expected to be magnified for the methylenethio analogue (**3**), considering the greater length of the carbon–sulfur bond as compared to the carbon–oxygen bond. These results are consistent with the relative activities of compounds **2**, **3**, and **20** (Table 2). However, if the atomic distance of the bridging atoms is an overriding factor that determines receptor binding activity, it is difficult to rationalize the lower affinity of the ethylene-bridged derivative **4**. In fact, from these results, it seems likely that factors other than bridge length significantly contribute to the differences observed in biological activities of this series. For example, it is possible that the shorter length of the sulfide bridge of **20** may provide a benefit to activity, but since the sulfur is directly attached to the heterocycle it may alter the electronic nature of the ring and lead to decreased activity. Therefore, a compound with intermediate receptor binding affinity results.

In addition to examining the effect of the bridging unit, the effect of altering the quinoline ring of compound **20** was examined. In some cases the structure–activity comparisons for the compounds summarized in Table 2 may be less than ideal due to multiple changes in the heterocycle; however, a few observations are noteworthy. For example, addition of a nitrogen to the 3-position of the quinoline ring reduced the receptor binding affinity (quinazoline **21**), while a 5-fold enhancement in activity was observed by the addition of a nitrogen to the 5-position of **20** (i.e., naphthyridine **22**). With an IC_{50} of 20 nM, naphthyridine **22** represented the most active compound in this series. This increased binding affinity presumably results from the additional interaction of the 5-nitrogen of the naphthyridine ring with the hydrogen binding pocket in the receptor model originally proposed by Duncia and co-workers.[14] Receptor binding affinity is diminished when the extra nitrogen of the heterocycle is moved to the opposite side of the ring, as in the case of pyrrolopyrimidine **24**. When the second ring is eliminated (pyridine **23**), activity is likewise reduced. Finally, blocking the function of other putative pharmacophores, such as the tetrazole N-H and the N-1 nitrogen of the quinoline (compounds **28** and **26**, respectively), abolished receptor binding affinities. Unfortunately, we could not ascertain which moiety of **26** (the sulfone or the *N*-oxide) had a negative impact on activity since we were unable to selectively oxidize compound **20** to give either the sulfone or the *N*-oxide exclusively.

The three most potent analogues in the receptor binding assay, **20–22**, were examined further for their ability to antagonize angiotensin II contraction of rabbit abdominal aortic rings. As illustrated in Figure 4, compounds **20–22** produced concentration-dependent reversal of angiotensin II contraction. Although these compounds were less potent than saralasin or losartan in this functional assay, the results are qualitatively consistent with their rank order potency with respect to their receptor binding affinities in rat liver membrane.

In summary, a synthetic entry into a series of (heteroarylthio)biphenylyltetrazoles was developed. The key steps involved the demethylation of a (methylthio)-

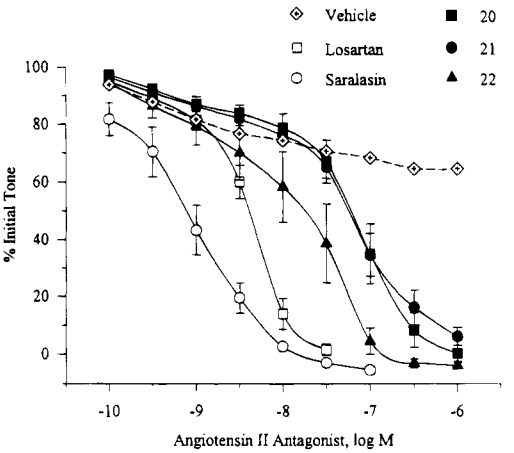


Figure 4. Concentration–response curves to angiotensin II antagonists in rabbit abdominal aorta denuded of endothelium and contracted with angiotensin II (2 nM). Data are means ± SEM. All compounds were given to rings from each animal (n = 3, vehicle n = 1).

biphenyl via a Pummerer rearrangement followed by reaction of the resulting sulfide with an electrophilic heteroaryl halide. The increased activity of quinoline **20** as compared to compound **3** indicated that the shorter thio bridge is preferred to the longer methylenethio linking unit. Molecular modeling studies indicated that the thio-bridged compound has an overlap with the losartan model compound (**29**) comparable to that of ICI-D8731 (**2**). Naphthyridine **22**, which incorporates an additional hydrogen bonding interaction, had an IC_{50} of 20 nM, which was approximately 5 times more potent than quinoline **20** but 4 times less potent than losartan at the angiotensin II receptor. This derivative was also less potent than losartan at reversing angiotensin II contraction of rabbit aorta.

Experimental Section

Chemistry: General. Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. Trimethyltin azide was prepared by the method of Chakravarty and Greenlee.[28] Anhydrous tetrahydrofuran (THF) was obtained from Aldrich Chemical Co. in a Sure/Seal bottle. All reactions involving air- or moisture-sensitive compounds were performed under a N_2 atmosphere. Flash chromatography[34] and flush chromatography were performed using EM Science silica gel 60 (230–400-mesh ASTM). The term "flush chromatography" refers to column chromatography when suction is applied to the bottom of the column to increase the flow rate of the eluant. Thin-layer chromatography (TLC) was performed with Whatman silica gel 60 Å MK6F TLC plates (250 μm). ^{1}H NMR spectra were determined with superconducting FT NMR spectrometers operating at 200 and 300 MHz. ^{13}C NMR were measured at 50.29 or 75.43 MHz. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. Significant ^{1}H NMR data are reported in the following order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), number of protons, and coupling constants in hertz. FT-IR spectra were recorded with an Analect FX6260 FT-IR spectrometer operating at 2 cm^{-1} resolution. Elemental analyses were performed by either Atlantic Microlab, Inc., Norcross, GA, or Galbraith Laboratories, Inc., Knoxville, TN. Chemical ionization mass spectra (CI-MS) were determined by Oneida Research Services, Whitesboro, NY. Fast atom bombardment mass spectra (FAB-MS) were recorded on a VG 70SQ mass spectrometer. Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected.

(4-(Methylthio)phenyl)boronic acid (6). A solution of 4-bromothioanisole (**5**) (24.4 g, 0.120 mol) in anhydrous THF

(100 mL) was placed under a N_2 atmosphere and cooled to −78 °C with a dry ice/acetone bath. To the 4-bromothioanisole solution was added slowly *n*-butyllithium (50.4 mL of a 2.5 M solution in hexanes, 0.130 mol, 1.1 equiv). The reaction mixture was allowed to stir for 15 min, and triisopropyl borate (33.2 mL, 0.140 mol, 1.2 equiv) was added. The reaction mixture was allowed to warm to room temperature over a 4 h period. The reaction was quenched by the addition of water, and the THF was removed with a rotary evaporator. The residual aqueous mixture was acidified to pH 1 (pH paper) by the addition of concentrated HCl. The resulting white solid was collected by filtration and washed with water. The solid was dried in a vacuum oven at 40 °C overnight to give 16.5 g (82%) of boronic acid **6** as a white solid. Mp: 205−208 °C (lit.[35] mp 209−209.5 °C). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 2.49 (s, 3), 7.23 (d, 2, J = 8.2), 7.40 (d, 2, J = 8.2), 8.01 (s, 2). ^{13}C NMR (DMSO-d_6, 75.43 MHz): δ 14.48, 122.12, 124.75, 134.95, 140.85. Anal. ($C_7H_9BO_2S$) C, H.

2-(4-(Methylthio)phenyl)benzonitrile (7). A solution of (4-methylthio)phenyl)boronic acid (**6**) (3.00 g, 17.85 mmol, 1.3 equiv), 2-bromobenzonitrile (2.49 g, 13.68 mmol, 1.0 equiv), and tetrakis(triphenylphosphine)palladium (0.21 g, 0.50 mmol, 0.01 equiv) in toluene (35 mL), ethanol (15 mL), and 2 M Na_2CO_3 (20 mL) was placed under a N_2 atmosphere and heated at reflux for 20 h. The reaction mixture was diluted with H_2O (150 mL) and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered, and concentrated with a rotary evaporator. The resulting brown oil was triturated with isooctane to give a brown solid. The solid was filtered, dissolved in EtOAc, and washed with 1 N NaOH. The organic layer was dried over Na_2SO_4, filtered, and concentrated with a rotary evaporator. The resulting solid was recrystallized from hexanes. The off-white solid was purified by flush chromatography on silica gel (95:5 hexanes/EtOAc) to give 1.94 g (63%) of nitrile **7** as a white solid. Mp: 84−84.5 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.54 (s, 3), 7.41 (dm, 2, J = 8.2), 7.53 (dm, 2, J = 8.2), 7.56 (m, 1), 7.62 (ddd, 1, J = 0.6, 1.3, 7.4), 7.78 (ddd, 1, J = 1.3, 7.4, 7.9), 7.94 (ddd, 1, J = 0.6, 1.3, 7.0). ^{13}C NMR (DMSO-d_6, 50.29 MHz): δ 14.53, 110.27, 118.89, 126.05, 128.36, 129.45, 130.25, 133.85, 134.18, 134.37, 139.77, 144.31. Anal. ($C_{14}H_{11}NS$) C, H, N, S.

4′-(Methylsulfinyl)-2-biphenylcarbonitrile (8). A solution of 2-(4-methylthio)phenyl)benzonitrile (**7**) (0.99 g, 4.39 mmol) in CH_2Cl_2 (50 mL) was placed under a N_2 atmosphere and cooled to −78 °C with a dry ice/acetone bath. To this solution was added 50−60% 3-chloroperoxybenzoic acid (1.29 g, 3.74−4.49 mmol, 0.85−1.02 equiv). The reaction mixture was stirred for 2 h, and an additional portion of 3-chloroperoxybenzoic acid (0.05 g, 0.14−0.17 mmol, 0.03−0.04 equiv) was added. The reaction mixture was stirred for 25 min and quenched by the addition of $Ca(OH)_2$ (0.51 g, 6.88 mmol, 1.6 equiv). The reaction mixture was stirred for 30 min at room temperature and filtered. The filtrate was concentrated with a rotary evaporator, and the resulting white solid was purified by flush chromatography on silica gel (1:1 EtOAc/hexanes followed by EtOAc) to give 0.90 g (83%) of nitrile **8** as a white solid. Mp: 114−115 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.80 (s, 3), 7.52 (m, 2), 7.66−7.83 (m, 6). ^{13}C NMR (DMSO-d_6, 75.43 MHz): δ 44.00, 111.21, 119.32, 125.05, 129.69, 130.57, 131.22, 134.62, 134.90, 140.92, 144.34, 147.84. Anal. ($C_{14}H_{11}NOS$) C, H, N, S.

General Procedure for Nitriles 10−14. A solution of 2-(4-methylthio)phenyl)benzonitrile (**7**) (1.23−4.00 g, 5.1−16.5 mmol, 1.0−1.1 equiv) in trifluoroacetic anhydride (20−50 mL) was placed under a N_2 atmosphere and heated at reflux for 30 min. The trifluoroacetic anhydride was removed with a rotary evaporator to give hemithioacetal acetate **9** as an oil. The oil was dissolved in a solution of 1:1 MeOH/Et_3N (20−100 mL) containing 1 equiv of an appropriate heteroaryl chloride (i.e., 4-chloroquinaldine,[36] 4-chloro-2-picoline,[36] 4-chloro-2-methylquinazoline,[37] 4-chloro-2-ethyl-1,5-naphthyridine,[38] and 4-chloro-2-methylpyrrolo[2,3-*d*]-pyrimidine[39]). The mixture was heated at reflux under N_2 for 1 h, and the solvent was removed with a rotary evaporator. The crude nitriles (**10**−**14**) were purified as indicated below.

4′-((2-Methyl-4-quinolinyl)thio)-2-biphenylcarbonitrile (10). The crude white solid obtained from hemithioacetal acetate **9**, and 4-chloroquinaldine was triturated with MeOH and filtered. The solid was dissolved in CH_2Cl_2, dried over Na_2SO_4, and filtered, and the solvent was removed with a rotary evaporator. The resulting solid was recrystallized from isooctane/CH_2Cl_2 to give 4.03 g (70%) of nitrile **10** as a white solid. Mp: 154.5−155.5 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.62 (s, 3), 6.92 (s, 1), 7.46−7.83 (m, 10), 8.03 (d, 1, J = 8.2), 8.22 (d, 1, J = 8.4). ^{13}C NMR (DMSO-d_6, 50.29 MHz): δ 25.01, 110.51, 118.68, 121.26, 123.75, 124.62, 126.72, 128.94, 129.38, 130.41, 130.49, 130.71, 131.53, 133.55, 133.94, 134.23, 138.68, 143.73, 145.01, 147.60, 158.62. Anal. ($C_{23}H_{16}N_2S$) C, H, N.

4′-((2-Methyl-4-quinazolinyl)thio)-2-biphenylcarbonitrile (11). The crude light yellow solid obtained from hemithioacetal acetate **9** and 4-chloro-2-methylquinazoline was dissolved in CH_2Cl_2 and washed sequentially with H_2O and 1 N NaOH. The organic layer was dried over Na_2SO_4, filtered, and concentrated with a rotary evaporator. The resulting solid was triturated with hot isooctane to give 2.30 g (73%) of nitrile **11** as a light yellow solid. An analytical sample was obtained by recrystallization from hexanes/CH_2Cl_2. Mp: 173−174 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.66 (s, 3), 7.46−7.97 (m, 11), 8.20 (d, 1, J = 8.4). ^{13}C NMR ($CDCl_3$, 50.29 MHz): δ 26.69, 111.82, 119.00, 121.80, 124.17, 127.15, 128.18, 128.66, 129.28, 129.86, 130.59, 133.45, 134.36, 134.41, 136.07, 139.48, 145.08, 149.58, 163.74, 170.60. Anal. ($C_{22}H_{15}N_3S$) C, H, N, S.

4′-((2-Ethyl-1,5-naphthyridin-4-yl)thio)-2-biphenylcarbonitrile (12). The crude light-brown solid obtained from hemithioacetal acetate **9** and 4-chloro-2-ethyl-1,5-naphthyridine was purified by flush chromatography on silica gel (2:3 EtOAc/hexanes). The light yellow solid was recrystallized from hexanes/CH_2Cl_2 and again from isooctane to give 0.65 g (38%) of nitrile **12** as a white solid. Mp: 133−134 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.16 (t, 3, J = 7.6), 2.75 (q, 2, J = 7.6), 6.76 (s, 1), 7.65 (dt, 1, J = 1.3, 7.6), 7.74−7.89 (m, 7), 8.20 (dd, 1, J = 1.3, 7.6), 8.35 (dd, 1, J = 1.6, 8.5), 8.96 (dd, 1, J = 1.6, 4.2). ^{13}C NMR (DMSO-d_6, 75.43 MHz): δ 14.01, 32.16, 111.33, 118.89, 119.30, 126.64, 129.71, 130.52, 131.10, 131.60, 134.62, 134.86, 136.84, 137.68, 140.08, 140.44, 142.74, 144.44, 150.15, 151.90, 164.44. Anal. ($C_{23}H_{17}N_3S$) C, H, N, S.

4′-((2-Methyl-4-pyridyl)thio)-2-biphenylcarbonitrile (13). The crude light-brown solid obtained from hemithioacetal acetate **9** and 4-chloro-2-picoline was dissolved in hot isooctane. The hot isooctane solution was decanted from some insoluble material, and the insoluble material was triturated with hot isooctane four additional times. The isooctane solutions were combined and allowed to cool. The solid precipitate that formed was collected by filtration, purified by flush chromatography on silica gel (3:2 EtOAc/hexanes), and recrystallized from isooctane/CH_2Cl_2 to give 1.54 g (41%) of nitrile **13** as colorless needles. Mp: 142−144 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.50 (s, 3), 6.88 (ddd, 1, J = 0.5, 1.9, 5.4), 6.95 (dt, 1, J = 0.5, 1.9), 7.49 (dt, 1, J = 1.3, 7.5), 7.55 (ddd, 1, J = 0.5, 1.3, 7.9), 7.63 (s, 4), 7.69 (ddd, 1, J = 1.3, 7.5, 7.9), 7.80 (ddd, 1, J = 0.5, 1.3, 7.5), 8.29 (d, 1, J = 5.4). ^{13}C NMR ($CDCl_3$, 75.43 MHz): δ 25.45, 112.26, 119.46, 119.78, 121.93, 129.14, 131.01, 131.11, 132.22, 134.04, 134.93, 135.63, 140.03, 145.20, 150.08, 150.16, 159.58. Anal. ($C_{19}H_{14}N_2S$) C, H, N, S.

4′-((2-Methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)thio)-2-biphenylcarbonitrile (14). The crude solid obtained from hemithioacetal acetate **9** and 4-chloro-2-methyl-7H-pyrrolo[2,3-*d*]pyrimidine was purified by flash chromatography on silica gel (2:3 EtOAc/hexanes followed by EtOAc). The resulting white solid was purified further by flash chromatography on silica gel (99:1 CH_2Cl_2/methanol) to give 0.54 g (34%) of nitrile **14** as a white solid. Mp: 240−241 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 3.34 (s, 3), 5.90 (dd, 1, J = 1.9, 3.5), 7.34 (dd, 1, J = 2.3, 3.5), 7.60−7.75 (m, 2), 7.70 (d, 2, J = 8.6), 7.79−7.90 (m, 1), 7.83 (d, 2, J = 8.6), 8.02 (ddd, 1, J = 0.4, 1.6, 7.8), 12.00 (br s, 1). ^{13}C NMR (DMSO-d_6, 75.43 MHz): δ 26.32, 99.18, 111.21, 113.80, 119.36, 126.48, 129.55, 130.49, 130.68, 131.08, 134.58, 134.89, 135.60, 139.44, 144.53, 152.15, 159.50, 159.90. Anal. ($C_{20}H_{14}N_4S$) C, H, N.

General Procedure for Tin Tetrazoles 15−19. A mixture of an appropriate nitrile (**10**−**14**) (0.35−2.00 g, 1.02−5.67

mmol), trimethyltin azide (0.42–1.75 g, 2.00–8.50 mmol, 1.0–2.0 equiv), and toluene (25–100 mL) was placed under a N_2 atmosphere and heated at reflux for 24–96 h. An additional portion of trimethyltin azide (0.42–0.99 g, 1.21–4.81 mmol, 0.7–2.0 equiv) was added, and the solution was heated at reflux for an additional 4–72 h. The mixture was cooled to 0 °C to room temperature and filtered to give the crude tin tetrazole. The tin tetrazoles **15–19** were hydrolyzed as indicated below to give tetrazoles **20–24**.

2-Methyl-4-((2′-(1*H*-tetrazol-5-yl)-4-biphenylyl)thio)-quinoline (20). Tin tetrazole **15** obtained from 4′-((2-methyl-4-quinolinyl)thio)-2-biphenylcarbonitrile (**10**) was dissolved in methanol (50 mL), and concentrated HCl (20 mL) was added. The precipitate that formed was collected by filtration and washed with ether to give 1.77 g (70%) of tetrazole **20** as a white solid. Mp: 180 °C dec. ^{1}H NMR (CD_3OD, 300 MHz): δ 1.17 (t, 3, J = 7.1), 2.84 (s, 3), 3.60 (q, 2, J = 7.1), 6.85 (s, 1), 7.43 (d, 2, J = 8.3), 7.65 (m, 4), 7.77 (tm, 2, J = 7.2), 7.94 (ddd, 1, J = 1.3, 6.9, 8.3), 8.11 (m, 2), 8.51 (d, 1, J = 8.4). ^{13}C NMR (CD_3OD, 75.43 MHz): δ 21.52, 118.25, 122.36, 123.92, 124.52, 124.60, 125.63, 129.56, 129.88, 131.40, 131.56, 132.18, 132.39, 135.28, 136.40, 137.93, 137.97, 141.11, 143.42, 156.48. IR (KBr): 3400, 2680, 1630, 1585 cm^{-1}. CIMS (CH_4, dep 50 MA/s): 255 (base), 396 (M + 1). Anal. ($C_{23}H_{17}N_5S$·HCl·0.9H_2O) C, H, N, S, H_2O.

2-Methyl-4-((2′-(1*H*-tetrazol-5-yl)-4-biphenylyl)thio)-quinazoline (21). Tin tetrazole **16** obtained from ((2-methyl-4-quinazolinyl)thio)-2-biphenylcarbonitrile (**11**) was hydrolyzed on silica gel and purified by flush chromatography (CH_2Cl_2 followed by 9:1 CH_2Cl_2/MeOH). The resulting yellow solid was triturated with CH_2Cl_2/MeOH and filtered to give 0.091 g (26%) of tetrazole **21** as a yellow solid. Mp: 199.5–201 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.53 (s, 3), 7.24 (d, 2, J = 8.4), 7.60 (d, 2, J = 8.4), 7.63–7.77 (m, 5), 7.88 (d, 1, J = 7.8), 7.96 (ddd, 1, J = 1.3, 6.8, 8.4), 8.18 (d, 1, J = 7.8). ^{13}C NMR (DMSO-d_6, 75.43 MHz): δ 26.79, 121.40, 124.34, 124.50, 127.21, 128.30, 128.84, 129.17, 130.63, 131.56, 131.63, 132.16, 135.44, 135.98, 141.35, 141.55, 149.42, 163.25, 170.22. CIMS (CH_4, dep 50 MA/s): 255 (base), 397 (M + 1). Anal. ($C_{22}H_{16}N_6S$·0.25H_2O) C, H, N.

2-Ethyl-4-((2′-(1*H*-tetrazol-5-yl)-4-biphenylyl)thio)-1,5-naphthyridine (22). Tin tetrazole **17** obtained from 4′-((2-ethyl-1,5-naphthyridin-4-yl)thio)-2-biphenylcarbonitrile (**12**) was dissolved in MeOH (5 mL), and concentrated HCl (2 mL) was added. The precipitate that formed was collected by filtration and recrystallized from MeOH/EtOAc to give 0.067 g (42%) of tetrazole **22** as a light-yellow solid. Mp: 206 °C dec. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.26 (t, 3, J = 7.6), 3.02 (q, 2, J = 7.6), 4.43 (br s, 1), 6.83 (s, 1), 7.37 (d, 2, J = 8.3), 7.66 (m, 2), 7.67 (d, 2, J = 8.3), 7.78 (m, 2), 8.04 (dd, 1, J = 4.2, 8.6), 8.64 (dd, 1, J = 1.6, 8.6), 9.11 (dd, 1, J = 1.6, 4.2). ^{13}C NMR (DMSO-d_6, 75.43 MHz): δ 14.29, 29.45, 118.85, 124.51, 127.13, 128.98, 129.48, 131.46, 131.55, 132.16, 132.84, 136.41, 136.92, 139.19, 141.27, 142.98, 151.94, 162.49. CIMS (CH_4, dep 50 MA/s): 255 (base), 411 (M + 1). Anal. ($C_{23}H_{18}N_6S$·HCl·0.5H_2O) C, H, N, S, Cl.

2-Methyl-4-((2′-(1*H*-tetrazol-5-yl)-4-biphenylyl)thio)pyridine (23). Tin tetrazole **18** obtained from 4′-((2-methyl-4-pyridyl)thio)-2-biphenylcarbonitrile (**13**) was hydrolyzed on silica gel and purified by flush chromatography (ether followed by 24:1 ether/MeOH). The resulting oil was dissolved in CH_2Cl_2, and 1 N ethereal HCl was added. The resulting solid was filtered and dried in a vacuum oven (0.1 Torr, 100 °C) to give 0.10 g (53%) of tetrazole **23** as a yellow solid. Mp: 121–124 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.53 (s, 3), 7.17 (m, 1), 7.18 (s, 1), 7.30 (d, 2, J = 8.2), 7.57 (d, 2, J = 8.2), 7.66 (m, 2), 7.75 (m, 2), 8.41 (d, 1, J = 6.4). ^{13}C NMR (DMSO-d_6, 75.43 MHz): δ 21.90, 119.80, 121.88, 124.47, 127.09, 129.45, 131.47, 131.59, 131.96, 132.18, 135.88, 141.14, 142.69, 144.36, 155.50, 155.92, 157.92. Anal. ($C_{19}H_{15}N_5S$·0.75HCl·0.25H_2O) C, H, N, Cl.

2-Methyl-4-((2′-(1*H*-tetrazol-5-yl)-4-biphenylyl)thio)-7*H*-pyrrolo[2,3-*d*]pyrimidine (24). Tin tetrazole **19** obtained from 4′-((2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-thio)-2-biphenylcarbonitrile (**14**) was suspended in ether, and trifluoroacetic acid was added. The solvent was removed with a rotary evaporator, and 1 N ethereal HCl was added to the residue . The resulting precipitate was collected by filtration and recrystallized from MeOH/ether. The solid was purified further by HPLC on a Waters C_{18}-μBondpack column (5:1 MeOH/H_2O), recrystallized from EtOH/H_2O, and dried in a vacuum oven (45 mTorr, 69 °C) to give 0.02 g (7%) of tetrazole **24** as a white solid. Mp: 226–228 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.49 (s, 3), 5.60 (q, 1, J = 1.8), 7.17 (d, 2, J = 8.2), 7.26 (dd, 1, J = 0.8, 2.5); 7.58 (d, 2, J = 8.2), 7.62 (m, 2), 7.80 (d, 2, J = 7.3), 11.90 (s, 1). ^{13}C NMR (DMSO-d_6, 100.58): δ 25.33, 98.57, 112.71, 125.39, 128.10, 128.12, 128.26, 129.77, 130.63, 130.65, 131.19, 134.61, 140.46, 140.69, 151.37, 158.82, 159.30. Anal. ($C_{20}H_{15}N_7S$·0.2HCl) C, H, N.

4′-((2-Methyl-4-quinolinyl)sulfonyl)-2-biphenylcarbonitrile *N*′-Oxide (25). A solution of 4′-((2-methyl-4-quinolinyl)thio)-2-biphenylcarbonitrile (**10**) (0.51 g, 1.45 mmol, 1 equiv) in CH_2Cl_2 (30 mL) was placed under a N_2 atmosphere and cooled to 0 °C with an ice bath. To this solution was added 50–60% 3-chloroperoxybenzoic acid (0.93 g, 2.7–3.2 mmol, 1.8–2.3 equiv). The reaction mixture was stirred for 2 days, and an additional portion of 3-chloroperoxybenzoic acid (0.46 g, 1.3–1.6 mmol, 0.89–1.1 equiv) was added. The reaction mixture was heated at reflux for 3 h and stirred at room temperature for 12 h, and an additional portion of 3-chloroperoxybenzoic acid (0.46 g) was added. The reaction mixture was heated at reflux for 4 h and filtered. To the filtrate was added a solution of $Ca(OH)_2$ in H_2O. The mixture was stirred at room temperature for 10 min and filtered. The filtrate was washed with 1 N NaOH, dried over Na_2SO_4, and filtered. The filtrate was concentrated with a rotary evaporator, and the resulting white foam was recrystallized from isooctane/CH_2Cl_2. The material was purified further by flush chromatography on silica gel (2:3 EtOAc/hexanes followed by 3:2 EtOAc/hexanes) to give 0.06 g (11%) of sulfone/*N*-oxide **25** as a white solid. Mp: 212 °C dec. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.78 (s, 3), 7.47 (dm, 1, J = 7.8), 7.52 (m, 1), 7.64–7.82 (m, 6), 7.73 (d, 2, J = 8.6), 8.12 (d, 2, J = 8.6), 8.31 (s, 1), 8.68 (dm, 1, J = 8.4), 8.79 (dm, 1, J = 8.4). ^{13}C NMR ($CDCl_3$, 75.43 MHz): δ 19.85, 112.22, 118.45, 121.39, 125.09, 126.03, 126.63, 129.03, 129.90, 130.23, 130.79, 130.98, 131.09, 132.09, 134.20, 135.07, 141.88, 143.59, 143.93, 144.55, 146.03. IR (KBr): 2227, 1343, 1324, 1153, 575 cm^{-1}. FAB MS (Magic Bullet, 8.441 mV): 119 (base), 401(M + 1). Anal. ($C_{23}H_{16}N_2O_3S$·0.5H_2O) C, H, N, S.

2-Methyl-4-((2′-(2-(triphenylmethyl)-1*H*-tetrazol-5-yl)-4-biphenylyl)thio)quinoline (26). A solution of tin tetrazole **15** (4.56 g, 8.16 mmol, 1.02 equiv), THF (15 mL), CH_2Cl_2 (50 mL), and 50% NaOH (1.0 mL) was stirred under a N_2 atmosphere for 20 min. Triphenylmethyl chloride (2.23 g, 8.00 mmol, 1 equiv) was added. The reaction mixture was allowed to stir at room temperature for 18 h, diluted with H_2O, and extracted twice with CH_2Cl_2. The organic layers were dried over Na_2SO_4, filtered, and concentrated with a rotary evaporator. The resulting white foam was recrystallized from isooctane/CH_2Cl_2 to give 3.48 g (68%) of (triphenylmethyl)tetrazole **26** as a white solid. Mp: 182–183 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.46 (s, 3), 6.73 (s, 1), 7.01 (d, 6, J = 7.1), 7.31 (m, 13), 7.51 (m, 4), 7.71 (ddd, 1, J = 1.5, 7.0, 8.4), 8.02 (m, 2), 8.20 (dd, 1, J = 1.3, 8.4). ^{13}C NMR ($CDCl_3$, 75.43 MHz): δ 25.19, 82.94, 119.08, 123,33, 124.43, 125.65, 126.28, 127.64, 127.94, 128.25, 128.42, 128.97, 129.81, 129.97, 130.10, 130.33, 130.45, 130.72, 134.09, 140.82, 141.09, 142.29, 147.24, 147.72, 158.25, 163.87. Anal. ($C_{42}H_{31}N_5S$) C, H, N.

2-Methyl-4-((2′-(1*H*-tetrazol-5-yl)-4-biphenyl)sulfonyl)-quinoline 1-Oxide (28). A solution of 2-methyl-4-((2′-(1-(triphenylmethyl)-1*H*-tetrazol-5-yl)-4-biphenylyl)thio)quinoline (**26**) (0.29 g, 0.45 mmol, 1 equiv) in CH_2Cl_2 (30 mL) was placed under a N_2 atmosphere and cooled to −78 °C with a dry ice/acetone bath. To this solution was added 50–60% 3-chloroperoxybenzoic acid (0.27 g, 0.78–0.94 mmol, 1.7–2.1 equiv). The reaction mixture was stirred for 4 h, and an additional portion of 3-chloroperoxybenzoic acid (0.27 g, 0.78–0.94 mmol, 1.7–2.1 equiv) was added. The reaction mixture was allowed to warm to room temperature over a period of 22 h and quenched by the addition of a saturated aqueous solution of $Ca(OH)_2$. The CH_2Cl_2 layer was separated and washed with 1 N NaOH (2×) and H_2O (1×). The CH_2Cl_2 layer was dried

over Na_2SO_4, filtered, and concentrated with a rotary evaporator. The resulting white glass was purified by flush chromatography on silica gel (4:1 hexanes/EtOAc followed by 4:3 hexanes/EtOAc) to give sulfone *N*-oxide **27**. The white solid was dissolved in CH_2Cl_2 (5 mL), and 1 N ethereal HCl was added. The resulting solid was collected by filtration to give 0.05 g (25%) of tetrazole **28** as a pale yellow solid. Mp: 167 °C dec. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.65 (s, 3), 7.33 (d, 2, J = 8.3), 7.53 (d, 1, J = 7.4), 7.64 (m, 2), 7.74 (m, 1), 7.80 (t, 1, J = 7.6), 7.89 (t, 1, J = 7.6), 8.20 (d, 2, J = 8.3), 8.45 (s, 1), 8.51 (d, 1, J = 8.2), 8.61 (d, 1, J = 8.6). ^{13}C NMR (DMSO-d_6, 75.43 MHz): δ 19.07, 120.64, 124.12, 124.36, 125.63, 127.30, 128.24, 129.83, 130.20, 130.40, 130.80, 131.23, 131.52, 131.72, 132.03, 132.15, 140.16, 140.34, 142.58, 145.88, 146.01. IR (KBr): 1338, 1315, 1153, 757, 585 cm^{-1}. FAB MS (Magic Bullet 10000 mV): 133 (base), 444 (M + 1). Anal. ($C_{23}H_{17}N_5O_3S$) C, H, N.

Angiotensin II Radioligand Binding Assay. The radioligand binding assay of Lynch *et al.*[30] was employed with modifications. The livers from Sprague–Dawley rats were dissected, cut into pieces, placed in ice-cold buffer A solution (2.5 mL/1g) (buffer A: 250 mM sucrose, 5 mM HEPES, 1 mm EGTA, pH 7.4) and homogenized by 10 passes with a Dounce homogenizer. The homogenate was diluted to 10% (w/v) with buffer A solution and centrifuged at 3500g for 10 min. The pellet was resuspended in buffer A solution (100 mL) and diluted to 10% (w/v). A portion of this suspension (10.4 mL) was mixed with Percoll (1.4 mL) in 15 mL tubes and centrifuged at 17000g for 30 min. The two distinct layers close to the top of the tube were harvested and washed with 5 times volume of buffer B solution (buffer B: 25 mM sucrose, 50 mM Tris, pH 8.0). The sample was centrifuged at 17000g for 30 min. The resulting pellet was resuspended in 10 mL of incubation solution A (50 mM Tris, 10 mM $MgCl_2 \cdot H_2O$, 100 mM NaCl, and 1 mM EGTA, pH 7.4) and homogenized with a polytron. Protein quantitation was determined with a Bio-Rad protein assay kit. The homogenate was diluted with the incubation solution (incubation solution A plus 0.1% BSA, and 0.1% bacitracin) to 2.5 μg protein/μL. The binding assay was performed using [Tyr-3,5-^{3}H(N)]angiotensin II (5-L-isoleucine) as ligand at a final concentration of 1 nM. Specific binding was defined as the total binding minus the nonspecific binding obtained in the presence of angiotensin II (5 μM). Test compounds were screened at 10 μM, and the concentrations that inhibited specific binding by 50% (IC_{50}'s) were determined. Using incubation buffer for all assay additions, the total assay volume was 0.5 mL. After a 30-min incubation at 30 °C in a polypropylene tube, the assay was stopped by the addition of 4 mL of a washing solution (50 mM Tris, 10 mM $MgCl_2 \cdot H_2O$, 1 mM EGTA, pH 7.4), and the solution was filtered through a GF/B filter. The filter was washed twice with 5 mL of the washing solution and bound with solid scintillant, and the radioactivity was determined with an LKB Betaplate scintillation counter.

Rabbit Isolated Artery Assay. Standard *in vitro* techniques for measurement of arterial isometric tension were used. Abdominal aortas were removed from male New Zealand white rabbits and cut into 3–4-mm rings. The endothelium was removed by inserting the tip of a forceps into the lumen and rolling the ring on moistened filter paper. The rings were suspended for measurement of isometric tension in physiological salt solution maintained at 37 °C and were gassed with 95% O_2/5% CO_2. The basal tension of the rings was 6 g. Following two contractions with 50 mM potassium chloride and a 30-min equilibration period, the rings were contracted with 2 nM angiotensin II. When a stable plateau was reached, a concentration–response curve was determined by cumulative addition of the test compounds in 0.5-log increments. Responses were calculated as a percent of angiotensin II induced tone. Solutions of saralasin and losartan were prepared in saline, compounds **20** and **22** were prepared in saline with 20% NaOH (0.1 N, v/v), and compound **21** was prepared in saline with 40% NaOH (0.1N, v/v). Vehicle was saline with 20 % NaOH (0.1N, v/v).

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