Dual Angiotensin II and Endothelin A Receptor Antagonists: Synthesis of 2′-Substituted N-3-Isoxazolyl Biphenylsulfonamides with Improved Potency and Pharmacokinetics

Natesan Murugesan,* Zhengxiang Gu, Leena Fadnis, John E. Tellew, Rose Ann F. Baska, Yifan Yang, Sophie M. Beyer, Hossain Monshizadegan, Kenneth E. Dickinson, Maria T. Valentine, W. Griffith Humphreys, Shih-Jung Lan, William R. Ewing, Kenneth E. Carlson, Mark C. Kowala, Robert Zahler, and John E. Macor

Discovery Chemistry and Metabolic and Cardiovascular Drug Discovery, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, New Jersey 08543-5400

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In a previous report we demonstrated that merging together key structural elements present in an AT_1 receptor antagonist (**1**, irbesartan) with key structural elements in a biphenylsulfonamide ET_A receptor antagonist (**2**) followed by additional optimization provided compound **3** (Figure 1) as a dual-action receptor antagonist (DARA), which potently blocked both AT_1 and ET_A receptors. Described herein are our efforts directed toward improving both the pharmacokinetic profile as well as the AT_1 and ET_A receptor potency of **3**. Our efforts centered on modifying the 2′-side chain of **3** and examining the isoxazolylsulfonamide moiety in **3**. This effort resulted in the discovery of **7** (Figure 1) as a highly potent second-generation DARA. Compound **7** also showed substantially improved pharmacokinetic properties compared to **3**. In rats, DARA **7** reduced blood pressure elevations caused by intravenous infusion of Ang II or big ET-1 to a greater extent and with longer duration than DARA **3** or AT_1 or ET_A receptor antagonists alone. Compound **7** clearly demonstrated superiority over irbesartan (an AT_1 receptor antagonist) in the normal SHR model of hypertension in a dose-dependent manner, demonstrating the synergy of AT_1 and ET_A receptor blockade in a single molecule.

Introduction

Despite the availability of a number of agents for treating hypertension, adequate control of blood pressure is still not achieved in over one-third of the hypertensive population.[1] Since hypertension is a major portent of future cardiovascular disease, there exists a significant medical need for an antihypertensive drug that is effective across a wide variety of patients as a monotherapy. The endogenous peptides angiotensin II (Ang-II) and endothelin I (ET-1) are powerful vasoconstrictors and mitogens, and both peptides have been implicated in the pathogenesis of hypertension and cardiovascular disease.[2] Elevated levels of Ang II promote the synthesis and vasoconstrictive action of ET-1, and elevated levels of ET-1 increase the synthesis vasoconstrictive action of Ang II, thus creating a positive dual-feedback mechanism and an excellent target for treating hypertension.[3]

A considerable body of preclinical evidence has shown that simultaneous antagonism of both the renin−angiotensin system (primarily mediated by Ang II via AT_1 receptors) and the endothelin system (primarily mediated by ET-1 via ET_A receptors) can produce a greater reduction in blood pressure and added cardiovascular benefit than antagonizing either system alone. For example, in a canine model of renovascular hypertension, the combination of an AT_1 receptor antagonist (losartan) with a ET_A/ET_B mixed antagonist (bosentan) produced a 40 mmHg reduction in mean blood pressure, compared to a 20 mmHg decrease with losartan alone.[4] In another study, using a rat model of hypertension and heart failure, the combination of losartan with an ET_A receptor antagonist (LU-135252) worked synergistically to return blood pressure, heart weight, and mortality levels to those of the nonhypertensive controls.[5] Similar synergistic benefits of dual AT_1 and ET_A receptor antagonism have been demonstrated in several other animal models of hypertension such as in DOCA-salt rats, spontaneously hypertensive rats (SHRs), and diabetic rats.[6] Thus, it is anticipated that dual AT_1 and ET_A receptor antagonism in humans could be more effective than current standard therapies for treating hypertension.

In a previous report we detailed the design and synthesis of compound **3** (BMS-248360, Figure 1), as a dual-action receptor antagonist (DARA), which potently blocked both AT_1 and ET_A receptors.[7] When dosed orally in rats, **3** decreased blood pressure in angiotensin-mediated (SHR) as well as in endothelin-mediated (DOCA-salt-treated rats) models of hypertension. Thus, compound **3** provided the proof-of-principle that a DARA compound would have a broader spectrum of antihypertensive activity when compared to individual AT_1 or ET_A receptor antagonists. However, while compound **3** was orally active in rats ($\%F_{rat} = 38$), it was not highly orally available in higher species such as dog ($\%F_{dog} = 6$) or cynomologus monkey ($\%F_{monkey} = 7$). Furthermore, as an AT_1 receptor antagonist, **3** was weaker than our AT_1 receptor antagonist standard, irbesartan (**1**, Figure 1), and as an ET_A receptor antagonist, **3** was weaker than BMS-193884 (**2**, Figure 1), our ET_A receptor antagonist standard. Consequently, we focused our attention on optimization studies to improve both the phar-

* To whom correspondence should be addressed. Phone: 609-818-5391. Fax: 609-818-3450. E-mail: natesan.murugesan@bms.com

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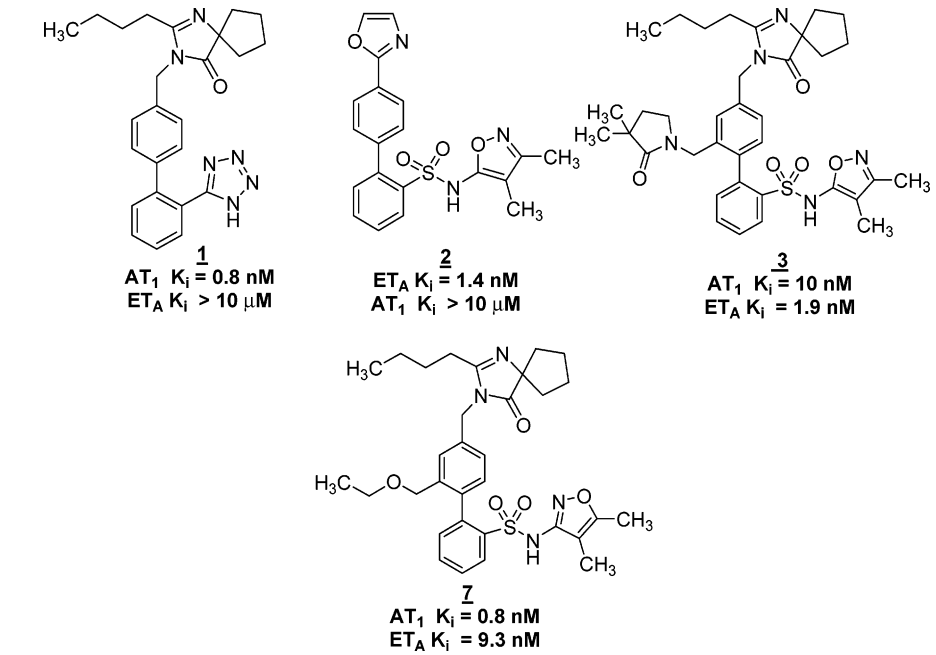
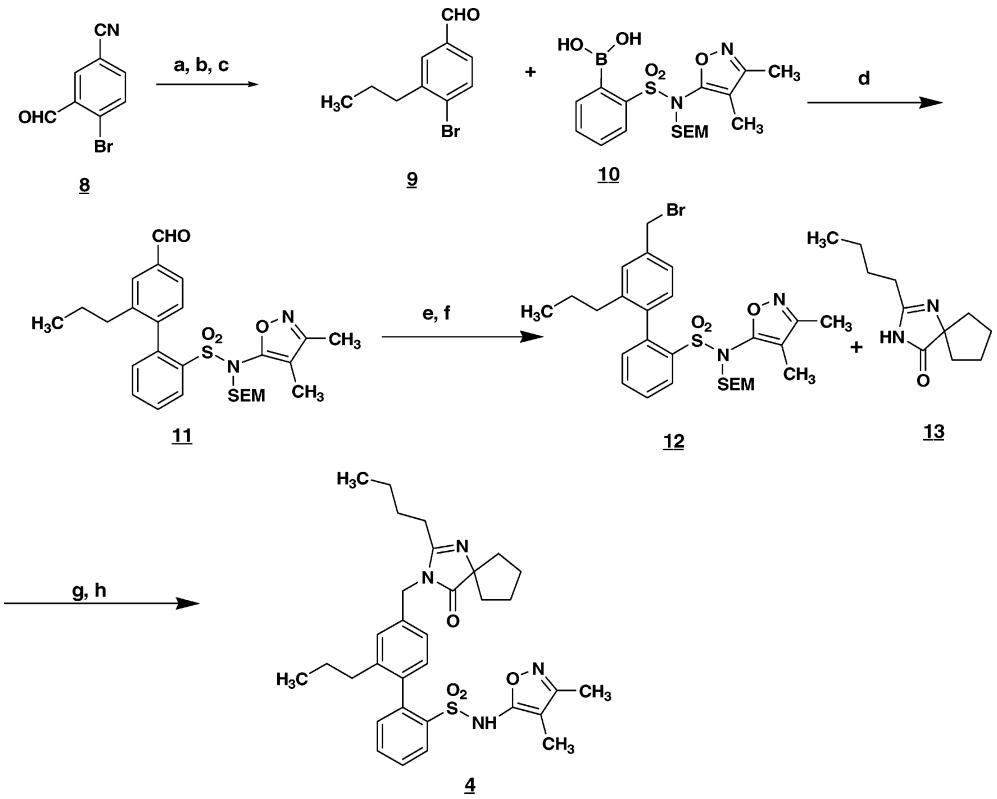


Figure 1.

Scheme 1[a]



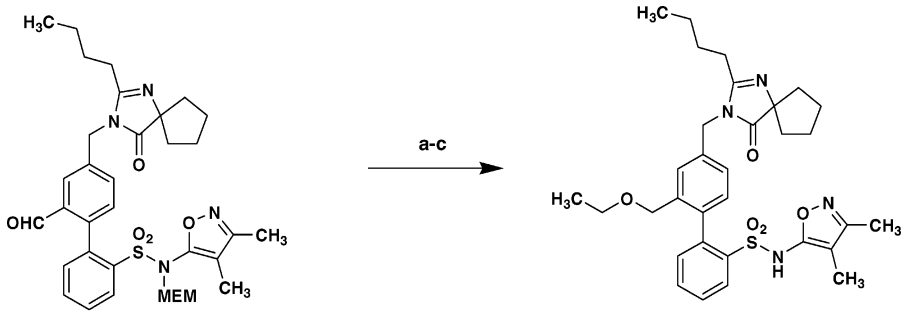
[a] (a) $EtPPh_3^+Br^-$, BuLi (83%); (b) H_2, PtO_2 (85%); (c) DIBAL-H, THF (90%); (d) compound **9**, $(Ph_3P)_4Pd$, aqueous Na_2CO_3, EtOH/toluene (52%); (e) $NaBH_4$, MeOH; (f) CBr_4, Ph_3P, DMF (82%, two steps); (g) compound **13**, NaH, DMF; (h) 6 N aqueous HCl/EtOH (64%, two steps).

macokinetic profile as well as the AT_1 and ET_A receptor potency of **3**. Our efforts centered on modifying the 2′-side chain of **3** and examining the isoxazolylsulfonamide moiety in **3**. This effort resulted in the discovery of **7** (BMS-346567, Figure 1) as a highly potent second-generation DARA, and herein we describe the design, synthesis, and pharmacological and pharmacokinetic properties of this compound.

Chemistry

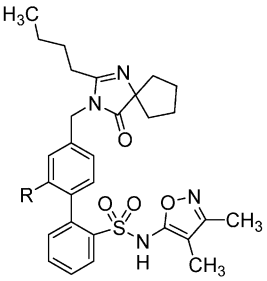
The syntheses of target compounds **4**−**7** were carried out in a manner similar to our previously published synthesis of **3**[7] (Schemes 1 and 2). The 2′-propyl derivative **4** was synthesized as shown in Scheme 1. Wittig olefination of aldehyde **8** using ethyltriphenylphosphonium bromide, followed by hydrogenation of the result-

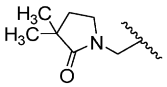
Scheme 2[a]



[a] (a) Triethylsilane, CH_2Cl_2 (77%); (b) ethyl iodide, AgO, DMF (49%); (c) 6 N aqueous HCl/EtOH (80%).

Table 1. SAR of 2′-Substituted *N*-5-Isoxazolyl Biphenylsulfonamide Derivatives



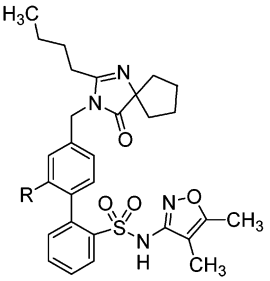
Compound	R	AT_1 K_i (nM) Rat	AT_1 K_i (nM) human	hET_A K_i (nM)	Oral AII Pressor (30μM/kg) (AUC units)	Oral big ET Pressor (30μM/kg) (AUC units)	Caco-2 cell monolayer permeability (nm/s)
1	-	0.8 ± 0.2	1.1 ± 0.3	$>10^4$	13,500	inactive	100
2	-	$>10^4$	$>10^4$	1.4 ± 0.2	Inactive	9,700	250
3		7.9 ± 1.0	10.0 ± 1.0	1.9 ±0.4	5,800	7.900	30
4	**-$CH_2CH_2CH_3$**	2.6 ± 1.0	5.1 ± 0.4	9.3 ± 2.1	15,900	8600	240
5	**-$CH_2OCH_2CH_3$**	1.4 ± 0.5	0.6 ± 0.2	5.4 ± 1.4	13,900	3,900	170

ing olefin in the presence of platinum oxide, and subsequent reduction of the nitrile group to the aldehyde derivative using DIBAL afforded the *n*-propyl derivative **9**. The boronic acid derivative **10** was prepared as described previously.[8] Suzuki coupling of **9** with **10** provided biphenyl **11**. Compound **11** was converted to the 4′-bromomethyl derivative **12** via reduction of the aldehyde to the benzyl alcohol using sodium borohydride, followed by conversion of the alcohol to the bromide using carbon tetrabromide and triphenyl phosphine. Treatment of **12** with the anion of the imidazolinone **13** followed by SEM deprotection afforded our desired 2′-propyl DARA analogue **4**.

Reduction of intermediate **14**[7] using triethylsilane (Scheme 2), followed by alkylation of the resulting alcohol with ethyl iodide in the presence of silver oxide, and subsequent deprotection of the MEM group using 6 N aqueous hydrochloric acid afforded the 2′-ethoxymethyl analogue **5** (Scheme 2).

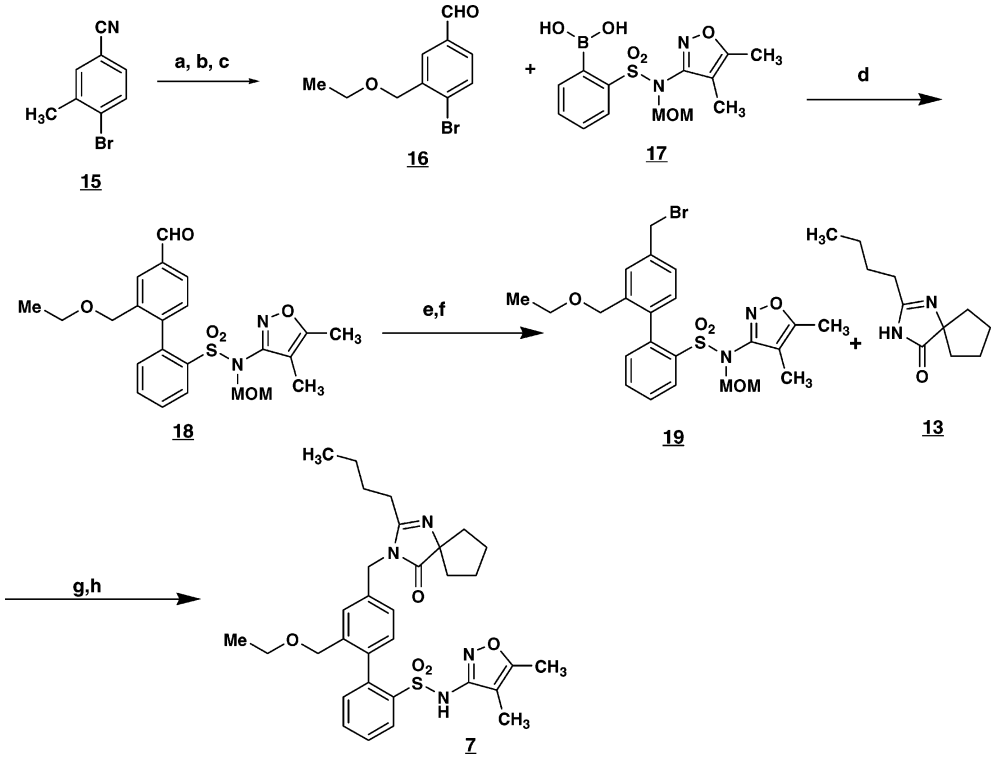
The syntheses of the corresponding aminoisoxazol-3-yl isomer of **4** (i.e., compound **6**, Table 2) was prepared using the identical sequence shown in Scheme 1 using the MOM-protected boronic acid derivative **17** (structure found in Scheme 3).[8] The syntheses of the corresponding aminoisoxazol-3-yl isomer of **5** (i.e., compound **7**) is shown in Scheme 3. Treatment of the nitrile **15** with *N*-bromosuccinimide in the presence of light, followed by treatment of the resulting bromide with sodium ethoxide in ethanol, followed by reduction of the nitrile to aldehyde using DIBAL afforded ether **16**. Suzuki

Table 2. SAR of 2′-Substituted *N*-3-Isoxazolyl Biphenylsulfonamide Derivatives



compound	R	AT_1 K_i (nM) rat	AT_1 K_i (nM) human	hET_A K_i (nM)	oral AII pressor (30 μM/kg) (AUC units)	oral big ET pressor (30 μM/kg) (AUC units)
1		0.8 ± 0.2	1.1 ± 0.3	$>10^4$	13 500	inactive
2		$>10^4$	$>10^4$	1.4 ± 0.2	inactive	9700
3		7.9 ± 1.0	10.0 ± 1.0	1.9 ± 0.4	5800	7900
6	$-CH_2CH_2CH_3$	3.2 ± 0.3	1.1 ± 0.1	6.5 ±1.5	16 300	13 000
7	$-CH_2OCH_2CH_3$	0.4 ± 0.2	0.8 ± 0.1	9.3 ±0.9	18 600	15 800

Scheme 3[a]



[a] (a) NBS, CCl_4; (b) NaOEt, EtOH (77% for two steps); (c) DIBAL-H, THF (80%); (d) compound **16**, $(Ph_3P)_4Pd$, aqueous Na_2CO_3, EtOH/toluene (82%); (e) $NaBH_4$, MeOH; (f) $(Ph)_3P$, CBr_4, DMF (90% for two steps); (g) compound **13**, NaH, DMF; (h) 6 N aqueous HCl/EtOH (79% for two steps).

coupling of **16** with the MOM-protected boronic acid **17** was effected using catalytic palladium tetrakistriphenylphosphine to yield biphenyl **18**. Reduction of the aldehyde in **18** using sodium borohydride in THF, followed by treatment of the resulting alcohol with triphenylphosphine and carbon tetrabromide, afforded the bromide **19**. Displacement of the bromide in **19** with the anion of imidazolinone **13**, followed by deprotection of the MOM group using aqueous 6 N HCl, then gave the 2′-ethoxymethyl DARA derivative **7** (Scheme 3). The resulting amorphous **7** was crystallized using 2-propanol/water to provide crystalline material, and an X-ray crystal structure was obtained (Figure 2).

Results and Discussion

In our previous report we demonstrated that merging together key structural elements present in an AT_1 receptor antagonist (**1**, irbesartan) with key structural elements in a biphenylsulfonamide ET_A receptor antagonist (**2**) provided a scaffold which had potent antagonist activity against both receptors. Introduction of a lactam moiety at the 2′-position of this scaffold afforded **3,** which was a potent and orally active dual-receptor antagonist (AT_1 K_i = 10 nM and ET_A K_i = 1.9 nM).[7] To study the in vivo hypertensive (pressor) effects of Ang-II and ET, these peptides can be injected directly into rats, causing substantial transient increases in

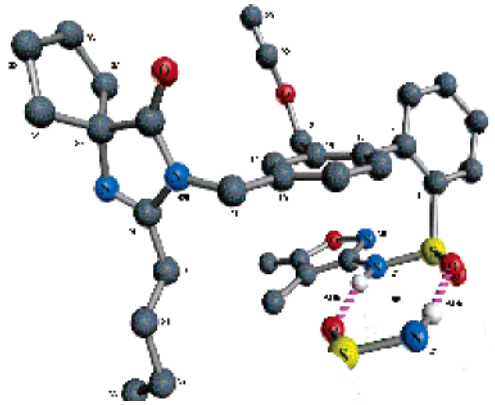


Figure 2. X-ray ORTEP of **7**.

blood pressure (BP). These effects can be blocked by pretreating the rats with either AT_1 or ET_A receptor antagonists, respectively. While irbesartan was active only in blocking the pressor effect of angiotensin II and **2** was active only in blocking bET-1 pressor effect, DARA **3** was uniquely effective as an inhibitor in both Ang II and bET-1 pressor studies when administered *orally*, indicating that dual antagonism of ET_A and AT_1 receptors could be achieved from a single compound in vivo. The oral bioavailability of **3** in rats was good (%F = 38) with excellent oral exposure (C_{max} = 3.1 μM at 6 mg/kg) and a reasonable elimination profile ($T_{1/2}$ = 5.5 h). However, in subsequent studies **3** showed less than 10% oral bioavailability in dogs and monkeys. These results prompted us to explore further the SAR around **3** with the goal of finding new DARA analogues with improved pharmacokinetic properties (i.e., improved oral bioavailability in dogs and monkeys) and improved dual-receptor potency. These studies were focused on eliminating potential sites of metabolism, reducing the molecular weight of our DARA compounds, and increasing their intestinal permeability.

In an effort to address these issues we focused on synthesizing analogues with lower molecular weights and a lower number of hydrogen-bond donor/acceptors compared to **3**, since molecular properties such as low MW and reduced number of H-bond donors/acceptors are important factors known to increase oral bioavailability of drug molecules. Due to the stringent structural requirements at the 4′-imidazolinone as well as isoxazolyl sulfonamide moieties, we initially focused our attention at the 2′-position of the molecule. A large number of 2′-substituted analogues of **3** were evaluated. These efforts resulted in the discovery of the 2′-propyl analogue **4** and the 2′-ethoxymethyl derivative **5** as potent DARA analogues. Both compounds were potent AT_1 and ET_A receptor antagonists in vitro, and both compounds were equivalent to (or superior to) irbesartan in the rat Ang II pressor model (Table 1). In the "big-ET" oral pressor model, 30 μmol/kg of **5** was 3-fold less potent when compared with 30 μmol/kg of BMS-193884, our standard ET_A receptor antagonist Table 1, while 100 μmol/kg of **5** had similar potency to 30 μmol/kg BMS-193884 (data not shown). In the Caco-2 cell permeability assay, **4** and **5** showed superior penetration compared to **3** (Table 1), and they were equivalent to compound **2**, a highly orally bioavailable compound in man. However, the oral bioavailabilities of **4** and **5** in monkeys were still low (%F < 5). Given the prediction of high permeability from the Caco-2 cell assay, first-pass metabolism was suspected as the cause of this poor oral bioavailability. A possible site of metabolism could be the 5-aminoisoxazole ring, since we had shown in our earlier work that this moiety is susceptible to presystemic metabolism, resulting from enzymatic cleavage of the 5-isoxazole ring by bacteria in the rat GI tract.[9] We had shown that analogues containing the 3-isoxazole regioisomer appeared to be resistant to this type of degradation of the isoxazole ring.

On the basis of the above analysis, analogous combinations of the 3-isoxazole with the 2′-propyl and 2′-ethoxymethyl substituents found in **4** and **5**, respectively, were prepared. Analogue **6**, the 3-isoxazole isomer of **4**, and analogue **7**, the 3-isoxazole regiomer of **5**, both showed excellent in vitro and in vivo potency against both AT_1 and ET_A receptors (Table 2). Significantly, **7** (hAT_1 K_i = 0.8 nM and hET_A K_i = 9.3 nM) was 12-fold more potent than **3** at the human AT_1 receptor but 5-fold less active than **3** for the human ET_A receptor. Both **6** and **7** showed no activity against AT_2 and ET_B receptor subtypes (K_i's > 10 μM, data not shown).

In conscious normotensive rats, compound **7** dose-dependently antagonized the Ang II-induced pressor response with an ED_{50} value of 0.8 μmol/kg iv and 3.6 μmol/kg po (Figure 3). It was found to be substantially more potent and longer acting than irbesartan in this model (Figure 3). As reported previously, ET antagonists such as **2** are inactive in this model. Compound **7** was also more efficacious and longer acting than **2** in the big ET-1-induced pressor model (Figure 4). Compound **7** was also more potent and longer acting than **3** in these two pressor models as measured by the AOC values. Similar levels of improved efficacy were also seen for **6** versus **3** in these two pressor models (data not shown).

On the basis of its promising in vitro and in vivo profile, **7** was chosen for additional evaluation. The pharmacokinetic profile of **7** is summarized in Table 3. Compound **7** showed good oral bioavailability in rats, dogs, and monkeys, averaging 40%, 86%, and 21% F, respectively. The PK profile was substantially improved compared to **3**, which showed less than 10% oral bioavailability in dogs and monkeys.

Normal spontaneously hypertensive rats (SHRs) are believed to model human essential hypertension. A number of important classes of antihypertensive drugs such as calcium channel blockers, β-blockers, ACE inhibitors, and AT_1 receptor antagonists have shown efficacy in this model as well as in the treatment of human essential hypertension. Using telemetrized SHRs, the ability of compound **7** to lower BP was compared to irbesartan in SHRs at increasing oral doses, starting at 10 μmol/kg/day (days 15−21) and going to 30 μmol/kg/day (days 22−28) and 100 μmol/kg/day (days 29−35) over a 36-day period (Figure 5). Compound **7** caused a significant lowering of blood pressure at the lowest dose tested (10 μmol/kg/day), but this effect was not distinguishable from the effects of irbesartan at the same dose (Figure 5). At 30 μmol/kg/day, **7** was more effective compared to controls *and* irbesartan (Figure 5). This trend continued throughout the remaining duration of the study. In fact, at 100 μmol/kg/day, **7**

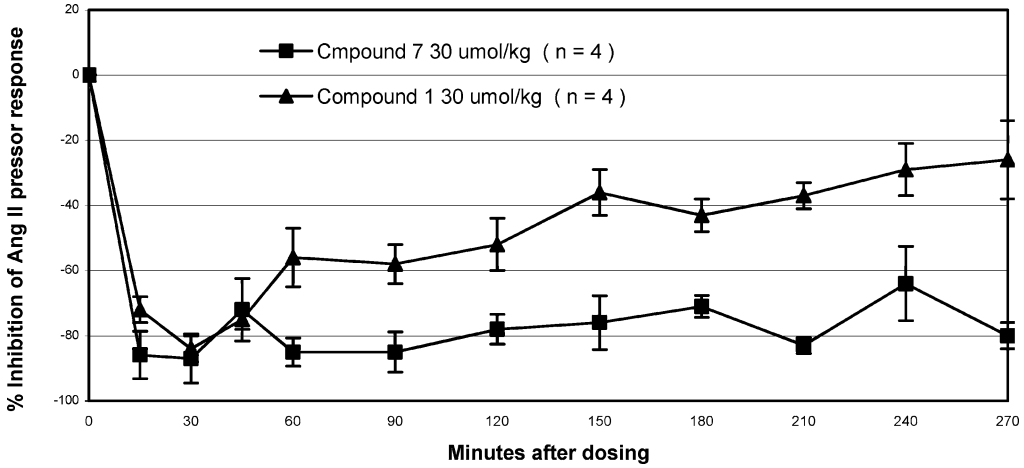


Figure 3. Effect of **7** (*po*, $n = 4$ per dose) and irbesartan (*po*, $n = 4$ per dose) on the Ang II pressor response up to 4 h after oral dosing. Compound **7** $AOC_{0-8h} = 18\,6000$ units; compound **1** (irbesartan) $AOC_{0-8h} = 11\,940$ units; compound **3** $AOC_{0-8h} = 6000$ units. Area over curve (AOC) indicates potency and duration of action.

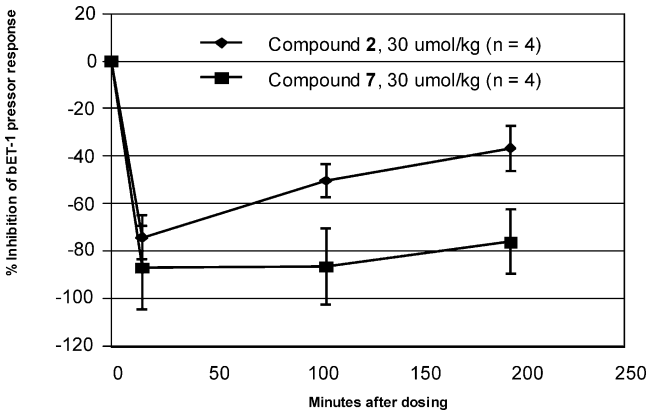
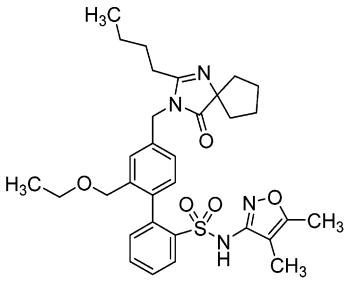


Figure 4. Effect of **2** (*po*) and **7** (*po*) on the bET-1 pressor response up to 3 h after oral dosing ($n = 4$ per dose). Compound **7** $AOC_{0-8h} = 15\,800$ units; compound **2** $AOC_{0-8h} = 10\,100$ units; compound **3** $AOC_{0-8h} = 7900$ units. Area over curve (AOC) indicates potency and duration of action.

Table 3. Pharmacokinetic Properties of 7[a]



7

species (dose in mg/kg)	rat (6)	dog (6.8)	monkey (6)
Cl (mL/kg/min)	1.9 ± 0.6	1.3 ± 0.5	13.2 ± 0.8
Vss (L/kg)	0.5 ± 0.05	0.2 ± 0.03	1.3 ± 0.5
plasma $T_{1/2}$ (h)	4.1 ± 0.6	2.4 ± 1.1	13.6 ± 1.1
mean residence time (h)	5.1 ± 1.1	2.3 ± 0.5	1.6 ± 0.5
C_{max} (μg/mL))	12 ± 3.1	11 ± 3	1.7 ± 0.9
T_{max} (h)	0.6 ± 0.4	0.7 ± 0.3	0.5 ± 0.2
oral bioavailability (%)	40	86	21

[a] Data are shown as mean ± SD ($n = 3$ all studies except monkey oral leg, which was $n = 5$).

reduced the blood pressure from 170 to less than 100 mmHg during the course of the drug's pharmacokinetic duration (Figure 6). The clear added efficacy of **7** in

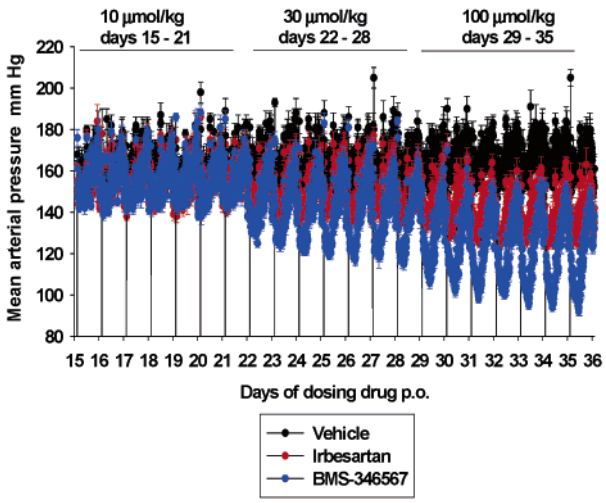


Figure 5. Effect of vehicle, irbesartan, and compound **7** on SHR mean arterial pressure at 10, 30, and 100 μmol/kg/day.

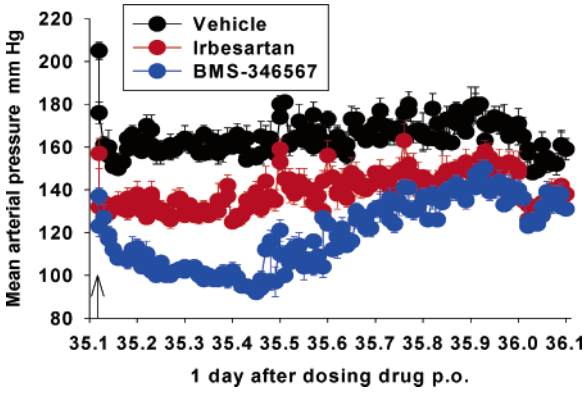


Figure 6. Effect of dosing irbesartan and **7** on mean arterial pressure in telemeterized SHR on the 7th day of dosing at 100 μmol/kg (day 35).

reducing blood pressure at the higher doses when compared to irbesartan is most likely attributable to the ET_A receptor antagonism found in **7** and lacking in irbesartan. In fact, on the last day of the study at 100 μmol/kg/day, the average BP of the SHRs treated with **7** was reduced by almost 70−90 mmHg for about 4 h, almost double the BP reduction achieved by irbesartan. Compound **7** at 100 μmol/kg/day essentially converted

the SHR into *normotensive* rats (Figure 6) during the course of its pharmacokinetic duration.

In summary, replacement of the bulky lactam moiety at the 2′-position of DARA **3** with smaller substituents, followed by replacement of the 5-isoxazole with the metabolically more stable 3-isoxazole, resulted in the discovery of **7** (BMS-346567). Compound **7** is a potent DARA (dual-acting receptor antagonist) analogue with substantially improved pharmacokinetic properties compared to **3**. In rats, DARA **7** reduced blood pressure elevations caused by intravenous infusion of Ang II or big ET-1 to a greater extent and with longer duration than DARA **3** or AT_1 or ET_A receptor antagonists alone. Compound **7** clearly demonstrated superiority over irbesartan (an AT_1 receptor antagonist) in the normal SHR model of hypertension in a dose-dependent manner, demonstrating the synergy of AT_1 and ET_A receptor blockade in a single molecule. Thus, compound **7** represents a potentially unique clinical opportunity as an antihypertensive because of its combined potent antagonism of both AT_1 and ET_A receptors.

Experimental Section

Melting points were recorded on a Thomas-Hoover capillary apparatus and are uncorrected. All chemical experiments were run under a positive pressure of argon. All solvents and reagents were used as obtained. Proton NMR (^{1}H NMR) and carbon NMR (^{13}C NMR) spectra were recorded on JEOL FX-270 and GX-400 spectrometers with tetramethylsilane as an internal standard. Chromatography was performed under flash conditions using EM Science silica with 0.040−0.063 mm particle size. Analytical and preparative HPLC were performed on YMC columns (S-5, 120A ODS, 4.6 × 150 mm; S-10, 120A ODS, 30 × 500 mm) with MeOH:water gradients containing 0.1% trifluoroacetic acid.

4-Bromo-3-propylbenzaldehyde (9). *n*-Butyllithium (2.5 M solution in hexane, 7.6 mL, 19 mmol) was added dropwise to a solution of ethyltriphenylphosphonium bromide (6.42 g, 17.3 mmol) in 100 mL of 1:1 THF/ether at −15 °C. The mixture was stirred for 3 h at room temperature and then cooled to −50 °C. A solution of 4-bromo-3-formyl-benzonitrile **8** (4.0 g, 19.0 mmol) in THF (10 mL) was added, and the mixture was allowed to warm to room temperature and stirred for 16 h. The mixture was added to water and extracted with EtOAc (3 × 150 mL), and the combined organic extracts were washed with water, dried over magnesium sulfate, and evaporated. The residue was chromatographed on silica gel using 95:5 hexane/EtOAc to afford 4-bromo-3-(1-propen-1-yl)benzonitrile as an *E*/*Z* mixture (3.5 g, 83%). A mixture of this material (1.5 g) and PtO_2 (150 mg) in EtOH (40 mL) was stirred under an atmosphere of hydrogen at 35 psi for 40 min. Filtration through a plug of Celite and concentration gave 1.44 g of 4-bromo-3-propylbenzonitrile (85%). DIBAL-H (1.0 M solution in toluene, 5.5 mL, 5.5 mmol) was added over 10 min to a solution of this material in toluene (20 mL) at −60 °C. The solution was allowed to warm to room temperature and stirred for 2 h. The mixture was then cooled to 0 °C, treated with excess MeOH, and stirred for 30 min. The white precipitate was filtered, and the filtrate was treated with aqueous 1 N HCl (50 mL). The mixture was stirred at room temperature for 10 min and then diluted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and finally evaporated to provide **9** (1.3 g, 90%) as an oil. ^{1}H NMR ($CDCl_3$): δ 1.00 (t, J = 7.3 Hz, 3H), 1.70 (m, 2H), 2.75 (m, 2H), 7.60−8.0 (m, 3H), 9.97 (s, 1H).

***N*-(3,4-Dimethyl-5-isoxazolyl)-4′-formyl-2′-propyl-*N*-[(2-trimethylsilyl)ethoxy]methyl][1,1′-biphenyl]-2-sulfonamide (11).** To a stirred solution of **9** (1.1 g, 4.8 mmol) and 2-borono-*N*-(3,4-dimethyl-5-isoxazolyl)-*N*′-(2-trimethylsilyl)-ethoxy]methyl)benzenesulfonamide **10**[8] (2.25 g, 5.28 mmol) in toluene (10 mL) and 95% EtOH (5 mL) under argon was added tetrakis(triphenylphosphine)palladium(0) (0.33 g, 0.28 mmol), followed by 2 M aqueous sodium carbonate (10 mL). The reaction mixture was heated at 85 °C for 2.5 h under argon, cooled, and diluted with EtOAc (100 mL). The organic layer was separated and washed with H_2O and brine, then dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel using 2:1 hexane/EtOAc to afford **11** (1.3 g, 52%) as a colorless gum. ^{1}H NMR ($CDCl_3$): δ 0.03 (m, 11H), 0.85 (m, 3H), 1.60 (m, 2H), 1.90 (s, 3H), 2.22 (s, 3H), 2.42 (m, 2H), 3.63 (m, 2H), 4.42 (m, 2H), 7.26−7.99 (m, 7H), 10.09 (s, 1H).

***N*-(3,4-Dimethyl-5-isoxazolyl)-4′-bromomethyl-2′-propyl-*N*-[(2-trimethylsilyl)ethoxy]methyl][1,1′-biphenyl]-2-sulfonamide (12).** To a stirred solution of 11 (1.3 g, 2.45 mmol) in MeOH (15 mL) was added $NaBH_4$ (74 mg, 1.96 mmol). The reaction was stirred at room temperature for 2 h and concentrated. The residue was diluted with EtOAc (200 mL), washed with water and brine, then dried over $MgSO_4$, and concentrated. The residue was dissolved in DMF (10 mL), and carbon tetrabromide (1.2 g, 3.6 mmol) was added, followed by triphenylphosphine (0.95 g, 3.6 mmol). The resulting mixture was stirred at 0 °C for 2 h, diluted with EtOAc, washed with water and brine, then dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel using 9:1 hexane/EtOAc to afford 12 (1.2 g, 82%) as a colorless gum. ^{1}H NMR ($CDCl_3$): δ 0.02 (m, 11H), 0.83 (m, 3H), 1.53 (m, 2H), 1.92 (s, 3H), 2.21 (s, 3H), 2.42 (m, 2H), 3.60 (m, 2H), 4.22 (m, 2H), 4.56 (s, 2H), 7.26−7.99 (m, 7H).

4′-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)-methyl]-*N*-(3,4-dimethyl-5-isoxazolyl)-2′-propyl[1,1′-biphenyl]-2-sulfonamide (4). NaH (202 mg, 60% in mineral oil, 5.05 mmol) was added to a stirred solution of 2-*n*-butyl-1,3-diazaspiro[4.4]non-1-en-4-one (13)[15] (466 mg, 2.02 mmol) in DMF (10 mL) at 0 °C. The resulting mixture was stirred at room temperature for 30 min and cooled to 0 °C. A solution of 12 (1.2 g, 2.02 mmol) in 2 mL of DMF was then added, and the mixture was stirred at room temperature for 3 h. The mixture was then diluted with EtOAc, washed with water and brine, then dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel using 1:4 hexane/EtOAc to afford 4′-[(2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)-methyl]-*N*-(3,4-dimethyl-5-isoxazolyl)-2′-propyl-*N*-[(2-trimethylsilyl)ethoxy]methyl][1,1′-biphenyl]-2-sulfonamide (1.2 g) as a gum.

This material was dissolved in 95% EtOH (25 mL), 6 N aq. HCl (25 mL) was added, and the resulting solution was heated at reflux for 1 h. The reaction mixture was concentrated, and the pH of the solution was adjusted to pH 8 using a saturated solution of sodium bicarbonate. The solution was then reacidified to pH 5 with glacial acetic acid, and the mixture was extracted with EtOAc. The combined organic extracts were washed with water and brine, then dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel using 1:4 hexane/EtOAc to afford **4** as a white solid (0.75 g, 64%, for two steps). ^{1}H NMR ($CDCl_3$): δ 0.81 (t, J = 7.3 Hz, 3H), 0.90 (t, J = 7.3 Hz, 3H), 1.37 (m, 2H), 1.48 (m, 2H), 1.64 (m, 2H), 1.86 (s, 3H), 1.95−2.23 (m, 11H), 2.35 (m, 2H), 2.80 (m, 2H), 4.90 (m, 2H), 7.01−7.85 (m, 7H). HRMS: $[M+H]^+$ calcd 577.2849, obsd 577.2843. Analysis ($C_{32}H_{40}N_4O_4S\cdot 0.3\ H_2O$).

4′-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)-methyl]-*N*-(3,4-dimethyl-5-isoxazolyl)-2′-ethoxymethyl-[1,1′-biphenyl]-2-sulfonamide (5). Triethylsilane (6 mL) and TFA (6 mL) were added to a solution of 4′-[(2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2′-formyl-*N*-(3,4-dimethyl-5-isoxazolyl)-*N*-[(2-methoxyethoxy)methyl][1,1′-biphenyl]-2-sulfonamide 14[7] (960 mg, 1.5 mmol) in 15 mL of dichloromethane at room temperature. The mixture was stirred for 2 h and then concentrated. The residue was taken up in ethyl acetate and washed successively with aqueous sodium bicarbonate, water, and brine. The organic layer was dried over sodium sulfate and concentrated. The residue was chromatographed on silica gel using 50:1 dichloromethane/methanol to afford 4′-[(2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-2′-

hydroxymethyl-*N*-(3,4-dimethyl-5-isoxazolyl)-*N*-[(2-methoxyethoxy)methyl][1,1′-biphenyl]-2-sulfonamide (740 mg, 77%) as a colorless gum. A mixture of this material (100 mg, 0.15 mmol), iodoethane (960 mg, 6.1 mmol), and silver(I) oxide (180 mg, 0.77 mmol) in 1.0 mL of DMF was heated at 40 °C for 16 h. Additional iodoethane (190 mg, 1.2 mmol) and silver(I) oxide (71 mg, 0.31 mmol) were added, and the reaction mixture was heated at 40 °C for an additional 4 h. The mixture was diluted with ethyl acetate, and the solution was then washed with water and brine. The organic layer was dried over sodium sulfate and then concentrated. The residue was chromatographed on silica gel using dichloromethane/methanol to afford a colorless gum (51 mg, 49%). This material was dissolved in 95% EtOH (2 mL), 6 N aq. HCl (2 mL) was added, and the resulting solution was heated at reflux for 2 h. The reaction mixture was concentrated, and the pH of the solution was adjusted to pH 8 using a saturated solution of sodium bicarbonate. The reaction solution was then reacidified to pH 5 with glacial acetic acid, and the mixture was extracted with EtOAc. The combined organic extracts were washed with water and brine, then dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel using 1:4 hexane/EtOAc to afford 5 in 80% yield as a white solid; mp 74−80 °C (amorphous). ^{1}H NMR ($CDCl_3$): δ 0.87 (t, J = 7 Hz, 3H), 0.99 (t, J = 7 Hz, 3H), 1.32 (m, 2H), 1.59 (m, 2H), 1.75−2.02 (m, 11H), 2.16 (s, 3H), 2.35 (m, 2H), 3.38 (m, 2H), 4.23 (m, 2H), 4.73 (s, 2H), 7.11−7.85 (m, 7H). MS *m/e* 593 (ESI+ mode). HRMS: $[M+H]^+$ calcd 593.2798, obsd 593.2770.

4′-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)-methyl]-*N*-(4,5-dimethyl-3-isoxazolyl)-2′-*n*-propyl-[1,1′-biphenyl]-2-sulfonamide (6). Compound 6 was prepared from the aldehyde 9 and the 3-aminoisoxazolyl boronic acid derivative 17 using a similar sequence as **4**. ^{1}H NMR ($CDCl_3$): δ 0.77 (t, J = 7.3 Hz, 3H), 0.89 (t, J = 7.3 Hz, 3H), 1.35 (m, 2H), 1.42 (m, 2H), 1.60 (m, 2H), 1.72−2.05 (m, 11H), 2.03−2.31 (m, 5H), 2.35 (m, 2H), 4.70 (m, 2H), 6.96−8.16 (m, 7H). ^{13}C NMR ($CDCl_3$): δ 6.67, 11.69, 14.14, 14.39, 22.74, 23.89, 26.51, 28.21, 29.23, 35.67, 37.83, 43.85, 105.38, 123.50, 127.52, 128.45, 130.12, 130.55, 132.58, 133.27, 137.33, 137.53, 137.84, 140.09, 143.19, 156.47, 162.10, 166.78, 187.22. Analysis ($C_{32}H_{40}N_4O_4S$) C, H, N, S.

4-Bromo-3-(ethoxymethyl)benzaldehyde (16). A mixture of ethyl 4-bromo-3-methylbenzonitrile **15** (19.6 g, 100 mmol), *N*-bromosuccinimide (17.8 g, 100 mmol), and benzoyl peroxide (0.58 g) in 500 mL of carbon tetrachloride was refluxed for 4 h. The mixture was then cooled to room temperature and filtered. The filtrate was concentrated, and the residue was chromatographed on silica gel using 2:1 hexanes/ethyl acetate to provide 4-bromo-3-bromomethylbenzonitrile (17 g) as a white solid. This material (8.67 g, 31.5 mmol) was then added to a freshly prepared solution of sodium ethoxide (2.25 g, 33.1 mmol) in DMF (3.5 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 16 h. The solution was concentrated and diluted with ethyl acetate. The mixture was then washed with water and brine, then dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica gel using 2:1 hexanes/ethyl acetate to provide 4-bromo-3-(ethoxymethyl)benzonitrile (5.85 g, 77%) as a colorless oil. DIBAL-H (1.0 M solution in hexane, 31.7 mL) was added over 10 min to a solution of this material in THF (160 mL) at −0 °C. The solution was allowed to warm to room temperature and stirred for 3 h. The mixture was then cooled to 0 °C and treated with 5 mL of MeOH and stirred for 5 min. The mixture was then poured into 150 mL of 0.5 N aqueous hydrochloric acid, and the mixture was then extracted with EtOAc. The organic layer was washed with water and brine, then dried over $MgSO_4$, and evaporated to provide **16** (4.74 g, 80%) as an oil. ^{1}H NMR ($CDCl_3$): δ 1.31 (t, J = 7 Hz, 3H), 3.66 (m, 2H), 4.59 (s, 2H), 7.60−8.0 (m, 3H), 9.99 (s, 1H).

***N*-(4,5-Dimethyl-3-isoxazolyl)-4′-formyl-2′-(ethoxymethyl)-*N*-(methoxymethyl) [1,1′-biphenyl]-2-sulfonamide (18).** To a stirred solution of **16** (3.8 g, 15.6 mmol) and 2-[[*N*-(4,5-dimethyl-3-isoxazolyl)-*N*-(methoxymethyl)amino]-sulfonyl]phenylbor onic acid **17**[9] (4.22 g, 12.4 mmol) in toluene (80 mL) and 95% EtOH (40 mL) under argon was added tetrakis(triphenylphosphine)palladium(0) (1.80 g, 1.56 mmol), followed by 2 M aqueous sodium carbonate (30 mL). The reaction mixture was heated at 85 °C for 3 h under argon, cooled, and diluted with EtOAc (200 mL). The organic layer was separated and washed with water and brine, then dried over $MgSO_4$, and concentrated. Silica gel chromatography using 2:1 hexanes/ethyl acetate provided **18** (5.9 g, 82%) as a colorless gum. ^{1}H NMR ($CDCl_3$): δ 1.15 (t, J = 7 Hz, 3H), 1.90 (s, 3H), 2.31 (s, 3H), 3.32 (s, 3H), 3.41 (m, 2H), 4.20−4.46 (m, 4H), 7.26−8.10 (m, 7H), 10.09 (s, 1H).

4′-(Bromomethyl)-*N*-(4,5-dimethyl-3-isoxazolyl)-2′-(ethoxymethyl)-*N*-(methoxymethyl) [1,1′-biphenyl]-2-sulfonamide (19). To a stirred solution of **18** (5.9 g, 12.87 mmol) in MeOH (150 mL) was added $NaBH_4$ (0.49 g, 12.87 mmol). The reaction was stirred at room temperature for 1 h and concentrated. The residue was diluted with EtOAc (200 mL), washed with water and brine, then dried, and concentrated. The residue was dissolved in DMF (60 mL). Carbon tetrabromide (6.83 g, 20.6 mmol) was added, followed by triphenylphosphine (5.4 g, 20.6 mmol). The resulting mixture was stirred at 0 °C for 3 h, diluted with EtOAc, washed with water and brine, then dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel using 4:1 hexane/EtOAc to afford **19** (6.07 g, 90%) as a colorless gum. ^{1}H NMR ($CDCl_3$): δ 1.13 (t, J = 7 Hz, 3H), 1.92 (s, 3H), 2.23 (s, 3H), 3.31 (s, 3H), 3.37 (m, 2H), 4.22 (m, 4H), 4.56 (s, 2H), 7.26−8.01 (m, 7H).

4′-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)-methyl]-*N*-(4,5-dimethyl-3-isoxazolyl)-2′-(ethoxymethyl) [1,1′-biphenyl]-2-sulfonamide (7). To a stirred solution of 2-*n*-butyl-1,3-diazaspiro[4.4]non-1-en-4-one (13)[7] (0.68 g, 2.94 mmol) in DMF (10 mL) at 0 °C, NaH (246 mg, 60% in mineral oil,6.15 mmol) was added. The resulting mixture was stirred at RT for 30 min and cooled to 0 °C. A solution of 19 (1.4 g, 2.67 mmol) in 3 mL of DMF was added, and the mixture was stirred at room temperature for 5 h. The mixture was then diluted with EtOAc, washed with water and brine, then dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel using 1:4 hexane/EtOAc to afford 4′-[(2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-*N*-(3,4-dimethyl-5-isoxazolyl)-2′-(ethoxymethyl)-*N*-methoxymethyl-[1,1′-biphenyl]-2-sulfonamide (1.36 g) as a gum.

This material was dissolved in 95% EtOH (30 mL), 6 N aq. HCl (30 mL) was added, and the resulting solution was heated at reflux for 2 h. The reaction mixture was concentrated, and the pH of the solution was adjusted to pH 8 using a saturated solution of sodium bicarbonate. The reaction solution was then reacidified to pH 5 with glacial acetic acid, and the mixture was extracted with EtOAc. The combined organic extracts were washed with water and brine, then dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel using 1:4 hexane/EtOAc to provide **7** as an amorphous white foam (1.0 g, 79% for two steps). A sample of this material was crystallized from 2-propanol/water to afford **7** as crystalline prisms; mp 148 °C. ^{1}H NMR ($CDCl_3$): δ 0.89(t, J = 7 Hz, 3H), 1.07(t, J = 7 Hz, 3H), 1.36(m, 2H), 1.62(m, 2H), 1.81−2.06(m, 11H), 2.26(s, 3H), 2.38(m, 2H), 3.37 (m, 2H), 4.17(m, 2H), 4.76-(s, 2H), 7.09−8.05 (m, 7H). ^{13}C NMR ($CDCl_3$): δ 6.73, 11.69, 14.15, 15.36, 22.73, 26.50, 28.20, 29.22, 37.79, 37.84, 43.78, 66.72, 70.35, 106.31, 125.21, 127.13, 128.65, 130.49, 130.73, 132.54, 133.20, 137.30, 137.47, 137.73, 138.15, 138.95, 156.81, 162.10, 166.85, 187.24. Analysis ($C_{32}H_{40}N_4O_5S\cdot 0.2\ H_2O$) C, H, N, S.

Radioligand Binding Studies. Angiotensin II. Human AT_1 receptor affinity was determined using a standard binding assay as previously described.[7,11]

Endothelin. Human ETA receptor affinity was determined using CHO-K1 cells expressing the human endothelin A receptor as described previously.[7]

In Vivo Rat Pressor Studies. Angiotensin II. Pressor studies were undertaken as described previously.[7] Rats were gavaged with vehicle, and immediately thereafter the first bolus (intravenous) iv injection of Ang II served as the control

pressor response. Irbesartan (30 μmol/kg) and compound **7** (30 μmol/kg) were given by oral gavage (po), and the rats were re-challenged with Ang II at various intervals up to 240 min. There were 6−8 rats per drug dose. The difference between the maximum blood pressure increase before and after drug was reported as the percent (%) inhibition of the Ang II pressor effect.

Endothelin. This study was performed as previously described.[7] Intravenous injection of big endothelin-1 (bET-1, 1.0 nmol/kg) into conscious normotensive rats causes a gradual and sustained increase in blood pressure that is inhibited by ET_A receptor antagonists. The initial ET-1 challenge was preceded by vehicle administration to establish a control response to the agonist. Compounds **2** (30 μmol/kg) and **7** (30 μmol/kg) were administered iv or po after control bigET-1 pressor response at various times after drug dosing. There were 6−8 rats per group.

Blood Pressure Measurements in Normal Telemeterized SHR. Male SHR (15 weeks old; Taconic Farms) were prepared for telemetry measurements of blood pressure and heart rate (Data Sciences International) as described previously.[14] Three groups of SHR were orally dosed with either vehicle, irbesartan, and compound **7** (9−11 rats per group). SHR received 1, 3, 10, 30, and 100 μmol/kg/day of irbesartan or compound **7** for 7 days at each dose for a total of 35 days of treatment. Blood pressure and heart rate were continuously monitored for the 35-day period. Blood pressure and heart rate differences between groups were tested with a linear model using SAS PROC MIXED, and Hochbergs's step-up procedure was applied to compensate for the multiple comparisons.

Caco-2 Cell Permeability Assay. This study was performed as previously described.[16]

Supporting Information Available: Results from elemental analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Moser, M. Is it time for a new approach to the initial treatment of hypertension? *Arch. Intern. Med.* **2001**, *161*, 1140−1144. (b) Sever, P. The heterogeneity of hypertension: why does not every patient respond to every antihypertensive drug? *J. Cardiovasc. Pharmacol.* **1998**, *31* (Suppl. 2), S1−S4. (c) Coca A. Actual blood pressure control: are we doing things right? *J. Hypertens.* **1998**, *16*, S45−51. (d) Waeber, B. Achieving blood pressure targets in the management of hypertension. *Blood Press.* **2001**, *2* (Suppl.), 6−12. (e) Gavras, H. P. Issues in hypertension: drug tolerability and special populations. *Am. J. Hypertens.* **2001**, *14* (Pt. 2), 231S−236S.

(2) (a) Yanagisawa, M.; Kurihara, H.; Kimura, S.; Tomobe, Y.; Kobayashi, M.; Mitsui, Y.; Yazaki, Y.; Goto, K.; Masaki, T. A novel potent vasoconstrictor peptide produced by vascular endothelial cells. *Nature (London)* **1988**, *332*, 411−415. (b) Inoue, A.; Yanagisawa, M.; Kimura, S.; Kasuya, Y.; Miyauchi, T.; Goto, K.; Masaki, T. The human endothelin family: three structurally and pharmacologically distinct isopeptides predicted by three separate genes. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 2863−2867. (c) Ferrario, C. M. The Renin-Angiotensin System: Importance in Physiology and Pathology. *J. Cardiovasc. Pharmacol.* **1990**, *15* (Suppl. 3), S1−S5. (d) Wexler, R. R.; Greenlee, W. J.; Irvin, J. D.; Goldberg, M. R.; Prendergast, K.; Smith, R. D.; Timmermans, P. B. M. W. M. Nonpeptide Angiotensin II Receptor Antagonists: The next Generation in Antihypertensive Therapy. *J. Med. Chem.* **1996**, *39*, 625−656.

(3) (a) Imai, T.; Hirata, Y.; Emori, T.; Yanagisawa, M.; Masaki, T.; Marumo, F. Induction of endothelin-1 gene by angiotensin and vasopressin in endothelial cells. *Hypertension* **1992**, *19*, 753−757. (b) Chua, B. H.; Chua, C. C.; Diglio, C. A.; Siu, B. B. Regulation of endothelin-1 mRNA by angiotensin II in rat heart endothelial cells. *Biochim. Biophys. Acta* **1993**, *1178*, 201−206.

(4) Massart, P. E.; Hodeige, D. G.; Van Mechelen, H.; Charlier, A. A.; Ketelslegers, J. M.; Heyndrickx, G. R.; Donckier, J. E. Angiotensin II and endothelin-1 receptor antagonists have cumulative hypotensive effects in canine Page hypertension. *J. Hypertens.* **1998**, *16*, 835−841.

(5) Bohlender, J.; Gerbaulet, S.; Kramer, J.; Gross, M.; Kirchengast, M.; Dietz, R. Synergistic effects of AT1 and ETA receptor blockade in a transgenic, angiotensin II-dependent, rat model. *Hypertension* **2000**, *35* (4), 992−997

(6) (a) Gardiner, S. M.; March, J. E.; Kemp, P. A.; Mullins, J. J.; Bennett, T. Hemodynamic effects of losartan and the endothelin antagonist, SB 209670, in conscious, transgenic ((mRen-2)27), hypertensive rats. *Br. J. Pharmacol.* **1995**, *116*, 2237−2244. (b) Dhein, S.; Hochreuther, S.; Spring, C. A. D.; Bollig, K.; Hufnagel, C.; Raschack, M. Long-term effects of the endothelinA receptor antagonist LU 135252 and the angiotensin-converting enzyme inhibitor trandolapril on diabetic angiopathy and nephropathy in a chronic type I diabetes mellitus rat model. *J. Pharmacol. Exp. Ther.* **2000**, *293* (2), 351−359. (c) Ikeda, T.; Ohta, H.; Okada, M.; Kawai, N.; Nakao, R.; Siegl, P. K. S.; Koybayashi, T.; Miyauchi, T.; Nishikibe, M. Antihypertensive effects of a mixed endothelin-A- and -B- receptor antagonists, J-104132, were augment in the presence of a AT1-receptor antagonist, MK-954. *J Cardiovasc. Pharmacol.* **2000**, *36*, S337−S341.

(7) Murugesan, N.; Tellew, J. E.; Gu, Z.; Kunst, B. L.; Fadnis, L.; Cornelius, L. A.; Baska, R. A. F.; Yang, Y.; Beyer, S. M.; Monshizadegan, H.; Dickinson, K. E.; Panchal, B.; Valentine, M. T.; Chong, S.; Morrison, R. A.; Carlson, K. E.; Powell, J. R.; Moreland, S.; Barrish, J. C.; Kowala, M. C.; Macor, J. E. Discovery of N-isoxazolyl biphenylsulfonamides as potent dual angiotensin II and endothelin A receptor antagonists. *J. Med. Chem.* **2002**, *45* (18), 3829−3835.

(8) Murugesan, N.; Gu, Z.; Stein, P. D.; Bisaha, S.; Spergel, S.; Girotra, R.; Lee, V. G.; Lloyd, J.; Misra, R. N.; Schmidt, J.; Mathur, A.; Stratton, L.; Kelly, Y. F.; Bird, E.; Waldron, T.; Liu, E. C. K.; Zhang, R.; Lee, H.; Serafino, R.; Abboa-Offei, B.; Mathers, P.; Giancarli, M.; Seymour, A. A.; Webb, M. L.; Moreland, S.; Barrish, J. C.; Hunt, J. T. Biphenylsulfonamide Endothelin Antagonists: Structure−Activity Relationships of a Series of Mono- and Disubstituted Analogs and Pharmacology of the Orally Active Endothelin Antagonist 2′-Amino-N-(3,4-dimethyl-5-isoxazolyl)-4′-(2-methylpropyl)[1,1′-bipheny l]-2-sulfonamide (BMS-187308). *J. Med. Chem.* **1998**, *41*, 5198−5218.

(9) Murugesan, N.; Gu, Z.; Spergel, S.; Young, M.; Chen, P.; Mathur, A.; Leith, L.; Hermsmeier, M.; Liu, E. C.-K.; Zhang, R.; Bird, E.; Waldron, T.; Marino, A.; Koplowitz, B.; Humphreys, W. G.; Chong, S.; Morrison, R. A.; Webb, M. L.; Moreland, S.; Trippodo, N.; Barrish, J. C. Biphenylsulfonamide Endothelin Receptor Antagonists. 4. Discovery of N-[[2′-[[(4,5-Dimethyl-3-isoxazolyl)-amino]sulfonyl]-4-(2-oxazolyl)[1,1′-biphenyl]-2-yl]methyl]-N,3,3-trimethylbutanamide (BMS-207940), a Highly Potent and Orally Active ETA Selective Antagonist. *J. Med. Chem.* **2003**, *46*, 125−137.

(10) Lee, J. Y.; Warner, R. B.; Brune, M. E.; Adler, A. L.; Winn, M.; De, B.; Zydowsky, T. M.; Opgenorth, T. J.; Kerkman, D. J.; DeBernardis, J. F. Cardiovascular effects of orally administered ABBOTT-81988, an angiotensin II antagonist, in conscious spontaneously hypertensive rats. *Am. J. Hypertens.* **1994**, *7*, 975−983.

(11) Dickinson, K. E. J.; Cohen, R. B.; Skwish, S.; Delaney, C. L.; Serafino, R. P.; Poss, M. A.; Gu, Z.; Ryono, D. E.; Moreland, S.; Powell, J. R. BMS-180560, an insurmountable inhibitor of angiotensin II-stimulated responses: comparison with losartan and EXP3174. *Br. J. Pharmacol.* **1994**, *113*, 179−189.

(12) Kitami, Y.; Hiwada, K.; Kokubu, T. Kidney renin gene expression in spontaneously hypertensive rats. *J. Hypertens.* **1989**, *7*, 727−731.

(13) Fujita, K.; Matsumura, Y.; Kita, S.; Miyazaki, Y.; Hisaki, K.; Takaoka, M.; Morimoto, S. Role of endothelin-1 and the ETA receptor in the maintainence of deoxycorticosterone acetate-salt-induced hypertension. *Br. J. Pharmacol.* **1995**, *114*, 925−930.

(14) Webb, R. L.; Navarrete, A. E.; Davis, S.; de Gasparo, M. Synergistic effects of combined enzyme inhibition and angiotensin II antagonism on blood pressure in conscious telemetered spontaneously hypertensive rats. *J Hypertens.* **1998**, *16*, 843−852.

(15) Bernhart, C. A.; Perreaut, P. M.; Ferrari, B. P.; Muneaux, Y. A.; Assens, J. L. A.; Clement, J.; Haudricourt, F.; Muneaux, C. F.; Taillades, J. E. A new series of imidazolones: highly specific and potent nonpeptide AT1 angiotensin II receptor antagonists. *J. Med. Chem.* **1993**, *36*, 3371−3380.

(16) Chong, S.; Dando, S. A.; Soucek, K. M.; Morrison, R. A. In vitro permeability through Caco-2 cells is not qualitatively predictive of in vivo absorption for peptide-like drugs absorbed via the dipeptide transporter system. *Pharm. Res.* **1996**, *13* (1), 120−123.

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