

Balanced AT₁/AT₂ Receptor Antagonists. 4.^{1,2} XR510 and Related 5-(3-Amidopropanoyl)imidazoles Possessing Equal Affinity for the AT₁ and AT₂ Receptors

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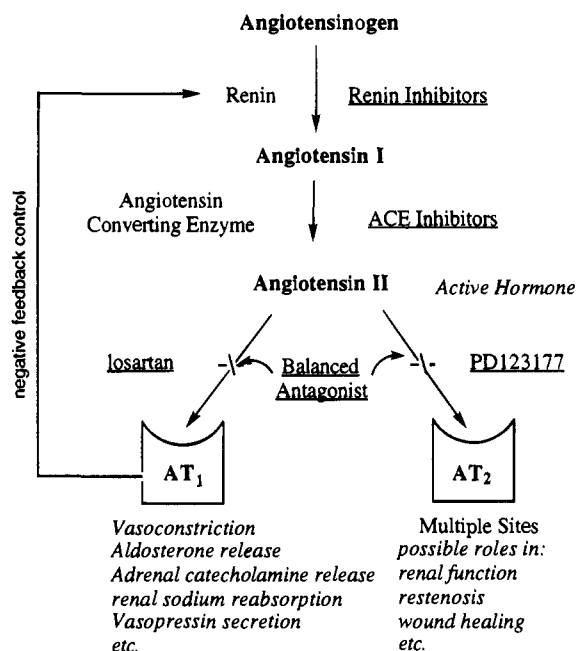
The identification of the AT₁ and AT₂ receptor subtypes has stimulated interest in developing balanced angiotensin II receptor antagonists. A series of 5-(3-amidopropanoyl)imidazoles has been prepared which possess balanced affinity for the AT₁ and AT₂ receptors. XR510 (1), 1-[[2'-[[[(isopentoxycarbonyl)amino]sulfonyl]-3-fluoro(1,1'-biphenyl)-4-yl]methyl]-5-[3-(*N*-pyridin-3-ylbutanamido)propanoyl]-4-ethyl-2-propyl-1*H*-imidazole, potassium salt, exhibits subnanomolar affinity for both receptor sites. XR510 is very active in lowering blood pressure in renal hypertensive rats and furosemide-treated dogs following oral administration.

Introduction

The renin–angiotensin system (RAS) is known to play an important role in cardiovascular regulation and the maintenance of blood pressure (Scheme 1).³ Angiotensin II (Ang II) is the active hormone of the RAS, and it mediates a variety of physiologic functions through stimulation of specific receptors. There are at least two distinct receptor subtypes^{4,5} designated as AT₁ and AT₂. The AT₁ receptor mediates most of the known Ang II physiologic functions, such as vasoconstriction and aldosterone release. The potential role for nonpeptide Ang II receptor antagonists in the treatment of hypertension has been well-demonstrated by AT₁-selective Ang II antagonists such as Cozaar (2, losartan, DuP 753, see Figure 1).⁶ The physiological functions of the AT₂ receptor are not clearly defined at this time, but AT₂ receptor-mediated effects of Ang II have been implicated in renal free water clearance,⁷ restenosis following vascular injury,⁸ collagen synthesis in cardiac fibroblasts,⁹ and the depressor response to angiotensin II and III in rats.¹⁰ These investigations have been facilitated by the discovery of the nonpeptide AT₂-selective receptor antagonists such as PD123177 (3).¹¹ It has been reported that blockade of the AT₁ receptor by losartan in animals and humans increased plasma levels of renin and Ang II.¹² This may act on the unblocked AT₂ receptors, although no unexpected effects attributable to AT₂ stimulation have been reported in animals and humans with losartan.¹³ Nevertheless, simultaneous inhibition of both receptors might be beneficial. In order to maintain potent antihypertensive activity while maximizing AT₂ blockade, we sought a nonpeptide antagonist with an IC₅₀ less than 10 nM for AT₁ and an AT₂/AT₁ ratio close to one.

Recently some compounds with affinity for both the AT₁ and AT₂ receptors have been described.¹⁴ The quinazolinone biphenyl tetrazole L-159,689 (4)^{14c} reported by the Merck research group has an IC₅₀ of 1.0 nM for the AT₁ receptor and 0.7 nM for the AT₂ receptor. The quinazolinone biphenyl sulfonylcarbamate L-162,393 (5)^{14d} showed similar affinity. Merck has also

Scheme 1. Renin–Angiotensin Cascade



reported a class of potent and balanced imidazopyridines such as L-162,620 (6)^{14b} with subnanomolar affinity for both receptors and an AT₂/AT₁ ratio of 2.8.

Our approach to balanced AT₁/AT₂ receptor antagonists was to build AT₂ affinity by structural modifications of our AT₁-selective biphenylimidazoles. The evolution of our AT₁-selective antagonists into balanced antagonists is illustrated in Scheme 2. Biphenyl "ortho" substitution on the inner phenyl ring of the AT₁-selective DMP 581 (7)¹⁵ provided compounds such as 8^{1a} with micromolar AT₂ affinity. When Merck scientists discovered that using certain acyl sulfonamides and sulfonylcarbamates as tetrazole replacements could increase AT₂ affinity,¹⁴ we combined "ortho" substitution with a sulfonylcarbamate as the acid isostere in the imidazole series and further improved AT₂ affinity 20–1000-fold (9).^{1a} Modification of the R⁵ substituent of the imidazole generated EXP597 (10),^{1c,16} which possessed balanced and nanomolar affinities for both receptors. However, poor oral activity and concern about possible

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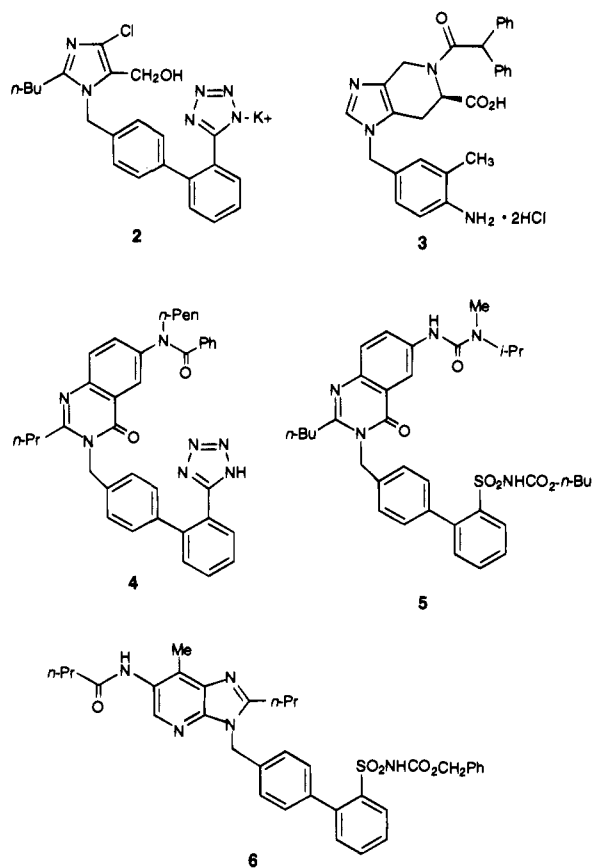
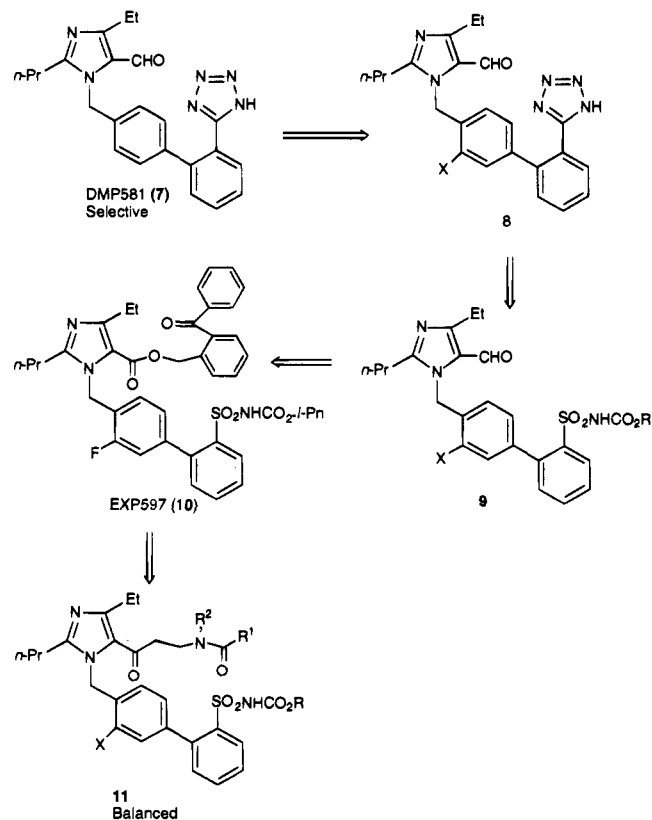


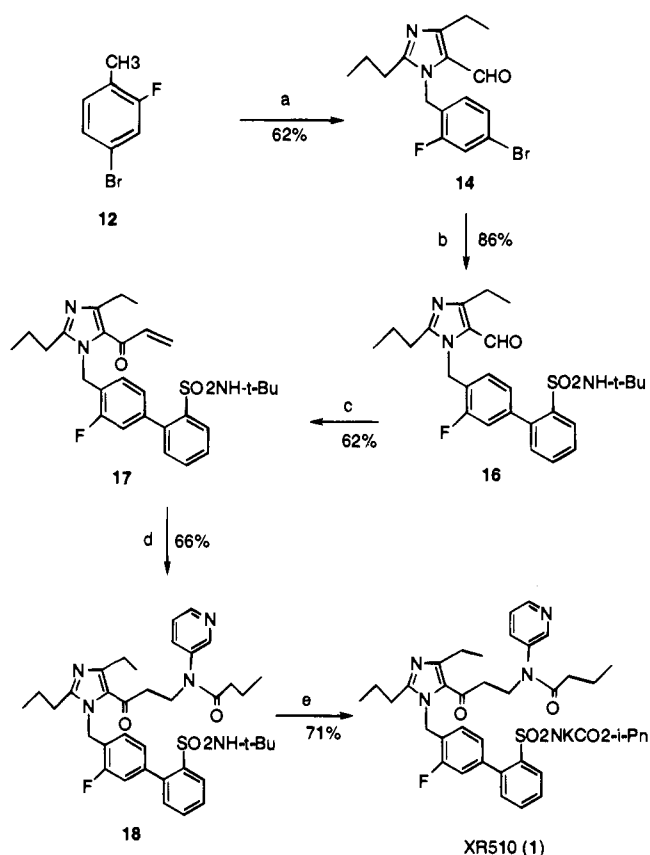
Figure 1. Structures of angiotensin II receptor antagonists.

Scheme 2. From AT₁ Selective to Balanced AT₁/AT₂ Antagonists



hydrolysis of the ester of EXP597 hindered further advancement of this compound. The 5-(3-amidopropanoyl)imidazoles (11) were designed in an attempt to solve the limitations of EXP597.

Scheme 3^a

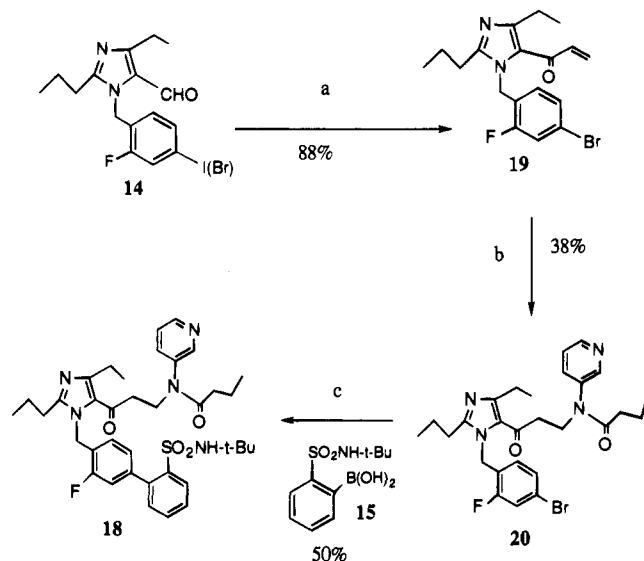


^a (a) (1) NBS/AIBN, (2) 4-ethyl-5-formyl-2-propyl-1*H*-imidazole (13), K₂CO₃/DMF; (b) [2-[(*tert*-butylamino)sulfonyl]phenyl]boronic acid (15), (PPh₃)₄Pd/Na₂CO₃; (c) (1) CH₂=CHMgBr, (2) MnO₂; (d) (1) 3-aminopyridine/Et₃N, (2) butyryl chloride/Et₃N; (e) (1) TFA, (2) *i*-PnOCOCl/pyridine/DMAP, (3) KOH.

Chemistry

A general procedure for synthesis of the 5-(3-amidopropanoyl)imidazoles (11) is demonstrated in Scheme 3 for the preparation of XR510 (1). Bromination of 4-bromo-2-fluorotoluene (12) followed by alkylation of imidazole 13¹⁵ yielded the (4-bromobenzyl)imidazole 14. Compound 14 was then coupled with boronic acid 15¹⁹ using tetrakis(triphenylphosphine)palladium(0) to provide the biphenylsulfonamide 16. The aldehyde moiety of 16 was converted to a vinyl ketone by reaction with vinylmagnesium bromide followed by oxidation with MnO₂ to furnish 17. Michael addition of 3-aminopyridine to the vinyl ketone of 17 followed by acylation with *n*-butyryl chloride afforded the 5-(propanamido) derivative 18. Treatment of 18 with TFA produced the primary sulfonamide which was then allowed to react with isopentyl chloroformate. The potassium salt, XR510 (1), was obtained by treatment of the sulfonyl-carbamate with potassium hydroxide.

Some of the 5-(3-amidopropanoyl)imidazoles (11) were prepared by the alternate route shown in Scheme 4. The aldehyde 14 was converted to vinyl ketone 19 by addition of vinylmagnesium bromide followed by oxidation with MnO₂. Michael addition of 3-aminopyridine to vinyl ketone 19 followed by acylation with *n*-butyryl chloride gave 20. Coupling of 20 with boronic acid 15 using tetrakis(triphenylphosphine)palladium(0) provided biphenylsulfonamide 18. The sulfonamide 18 was then converted to 11 by the same method described in Scheme 3.

Scheme 4^a

^a (a) (1) $\text{CH}_2=\text{CHMgBr}$, (2) $\text{MnO}_2/\text{CH}_2\text{Cl}_2$; (b) (1) 3-aminopyridine/ Et_3N , (2) butyryl chloride/ Et_3N ; (c) $(\text{PPh}_3)_4\text{Pd}$ /aqueous Na_2CO_3 , toluene.

Results and Discussion

It was found from our earlier work that certain combinations of AT_2 -enhancing modifications provide "additive" effects.¹ We have previously reported on balanced AT_1/AT_2 receptor antagonists obtained by the combination of "ortho" substitution on the inner phenyl ring of the biphenyl and replacement of the tetrazole group with a sulfonylcarbamate moiety.^{1a} Those compounds showed nanomolar affinities for both receptors and good AT_2/AT_1 ratios in our original binding assay⁵ where the radioligand [^{125}I]Ang II was used. From our collaboration with the Merck Research Laboratories in the Ang II area, we found later that the binding affinities changed when subjected to modified assay conditions¹⁷ in which the radioligand [^{125}I][Sar¹,Ile⁸]Ang II was employed. The different affinities observed from the two sets of assays are likely due to the difference in radiolabeled ligands, buffers, temperature, and receptor tissue preparations. The binding affinities obtained from the original and modified assay conditions are compared in Table 1 for three representative compounds. For most compounds tested in the modified assay, the AT_1 affinity increases by about 1 order of magnitude while the AT_2 affinity decreases by about 1 order of magnitude. Therefore, there is a greater difference between the AT_1 and AT_2 affinities or a larger AT_2/AT_1 ratio using the modified conditions. The more challenging modified assay conditions were employed for the evaluation of all subsequent compounds. Therefore, further improvement in AT_2 affinity was pursued.

The binding affinities of a series of 5-(3-(amidopropanoyl)imidazoles are summarized in Table 2. Subnanomolar affinity for the AT_1 receptor was observed for these compounds. To obtain subnanomolar affinity for the AT_2 receptor, the R^1 group must be aryl, as shown by compounds **27** and **28** which possessed subnanomolar activities for both receptors and AT_2/AT_1 IC_{50} ratios of less than one. However, **27** and **28** showed only modest oral activity as demonstrated by their oral ED_{30} values.

To improve the oral activity of this series of compounds, the phenyl groups were replaced with pyridyl

Table 1. Comparison of Binding Affinities in Original and Modified Assay Conditions^a

| compd | assay | IC_{50} (nM) ^b | | AT_2/AT_1 ratio |
|--------------------|------------------------|------------------------------------|---------------|---------------------------------|
| | | AT_1 | AT_2 | |
| 21 (EXP929) | original ⁵ | 3 | 7 | 2.3 |
| | modified ¹⁷ | 0.16 | 37 | 231 |
| 22 (EXP970) | original | 1 | 3 | 3 |
| | modified | 0.1 | 40 | 400 |
| 23 (EXP408) | original | 1 | 1 | 1 |
| | modified | 0.09 | 10 | 111 |

^a These three compounds were previously reported. See ref 1a. ^b Inhibitory concentration of potential Ang II antagonists which gives 50% displacement of the total specifically bound [^{125}I]Ang II,³ or [^{125}I][Sar¹,Ile⁸]Ang II. All compounds were tested in duplicate and were compared with DuP 753 and saralasin as internal standards. The intraassay and interassay variabilities are 5% and 20%, respectively.

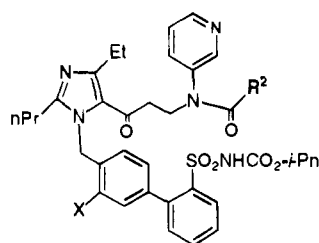
Table 2. Binding Affinities

| compd | R^1 | R^2 | IC_{50} (nM) ^a | | AT_2/AT_1 ratio | ED_{30} (mg/kg) po^b |
|-----------|------------------|------------------|------------------------------------|---------------|---------------------------------|--|
| | | | AT_1 | AT_2 | | |
| 24 | <i>n</i> -propyl | <i>n</i> -propyl | 0.20 | 5.0 | 25 | not tested |
| 25 | <i>n</i> -propyl | phenyl | 0.20 | 4.0 | 20 | <3.0 |
| 26 | <i>n</i> -butyl | phenyl | 0.30 | 10 | 33 | not tested |
| 27 | phenyl | phenyl | 0.25 | 0.18 | 0.70 | 1.57 |
| 28 | phenyl | <i>n</i> -propyl | 0.20 | 0.15 | 0.75 | 1.50 |
| 29 | phenyl | phenyl | 0.10 | 0.06 | 0.60 | 1.6 |
| 30 | phenyl | 4-pyridyl | 0.40 | 0.1 | 0.25 | <3 |
| 31 | 3-pyridyl | 4-pyridyl | 0.70 | 1.0 | 1.4 | 0.4 |
| 32 | 3-pyridyl | 3-pyridyl | 0.50 | 0.22 | 0.44 | 0.26 |
| 33 | 2-pyridyl | 3-pyridyl | 0.52 | 0.16 | 0.31 | 0.9 |
| 34 | 3-pyridyl | <i>n</i> -propyl | 0.32 | 0.25 | 0.78 | 0.27 |
| 35 | 3-pyridyl | isopropyl | 0.30 | 1.0 | 3.3 | not tested |
| 36 | 3-pyridyl | ethyl | 0.45 | 0.49 | 1.09 | 0.26 |
| 37 | 3-pyridyl | methyl | 0.40 | 3.0 | 7.5 | not tested |

^a Inhibitory concentration of potential Ang II antagonists which gives 50% displacement of the total specifically bound [^{125}I]-[Sar¹,Ile⁸]Ang II.¹⁷ All compounds were tested in duplicate and were compared with DuP 753 and saralasin as internal standards. The intraassay and interassay variabilities are 5% and 20%, respectively. ^b Effective dose to lower blood pressure by 30 mmHg in renal hypertensive rats (RHR).¹⁹ Determined by using the potassium salts of the corresponding acids.

groups. For compounds where $\text{R}^1 = \text{R}^2 = \text{phenyl}$, replacement of R^2 with 4-pyridyl did not improve oral potency (**30**). When both phenyl groups were replaced, the oral ED_{30} s were less than 1 mg/kg (**31–33**). Placing a 3-pyridyl group at R^2 resulted in a compound (**32**) which is 5 times more potent for the AT_2 receptor than the derivative with a 4-pyridyl group (**31**). When R^1 is 2- or 3-pyridyl (**33** or **32**), similar AT_2/AT_1 IC_{50} ratios

Table 3. "Ortho" Substitution Effect



| compd | X | R ² | IC ₅₀ (nM) ^a | | AT ₂ /AT ₁ IC ₅₀ ratio |
|-------|---|------------------|------------------------------------|-----------------|---|
| | | | AT ₁ | AT ₂ | |
| 34 | F | <i>n</i> -propyl | 0.32 | 0.25 | 0.78 |
| 38 | H | <i>n</i> -propyl | 0.40 | 1.0 | 2.5 |
| 32 | F | 3-pyridyl | 0.50 | 0.22 | 0.44 |
| 39 | H | 3-pyridyl | 0.30 | 1.0 | 3.3 |

^a Inhibitory concentration of potential Ang II antagonists which gives 50% displacement of the total specifically bound [¹²⁵I]-[Sar¹,Ile⁸]Ang II.¹⁷ All compounds were tested in duplicate and were compared with DuP 753 and saralasin as internal standards. The intraassay and interassay variabilities are 5% and 20%, respectively.

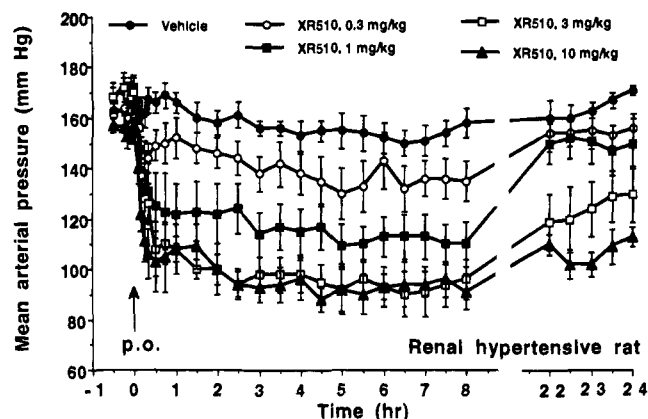


Figure 2. Effects of vehicle (0.05 mg/mL Na₂CO₃ in 0.5% methocel) and XR510 given po on mean arterial pressure in conscious renal hypertensive rats. Values represent the means \pm SEM and $n = 6-9$ per group.

were obtained, but the 3-pyridyl derivative **32** had better oral potency as shown by its ED₃₀ value. For compounds where R¹ is 3-pyridyl and R² is alkyl, the *n*-propyl (**34**) and ethyl (**36**) derivatives showed the best *in vitro* and *in vivo* profiles. Branched- (e.g. isopropyl) and shorter-chain (e.g. methyl) R² substituents yielded compounds with 4–10-fold higher AT₂/AT₁ IC₅₀ ratios (**35** and **37**).

The importance of the "ortho" substitution effect in this series was also investigated, and the results are shown in Table 3. While the AT₁ affinities were similar, the AT₂ potencies were improved by 4-fold for the fluoro-substituted analogs (**32** and **34**). This effect is important for obtaining balanced activity.

XR510 (**1**),^{2,18} the potassium salt of compound **34**, was chosen to undergo further pharmacological evaluation. In a rat adrenal membrane preparation,¹⁷ XR510 inhibited the specific binding of [¹²⁵I][Sar¹,Ile⁸]Ang II to the AT₁ and AT₂ receptors with IC₅₀s of 0.32 and 0.25 nM, respectively. In conscious renal hypertensive rats,¹⁹ XR510 decreased blood pressure with an oral ED₃₀ of 0.27 mg/kg and with a duration of action of greater than 24 h (Figure 2). XR510 is also very active in lowering blood pressure in conscious furosemide-treated dogs^{18,19}

with an oral ED₃₀ of 1 mg/kg; the duration of action was greater than 8 h.

Conclusion

We have discovered a series of 5-(3-amidopropanoyl)-imidazoles (**11**) possessing potent and balanced affinity for the AT₁ and AT₂ receptor subtypes. The best compounds in this series are ortho-substituted biphenyl sulfonylcarbamates containing a 5-(3-amidopropanoyl) group at the 5-position of the imidazole. These compounds are very active in lowering blood pressure in renal hypertensive rats following iv and po administration. Our leading candidate, XR510 (**1**), exhibited subnanomolar affinity for both receptors. It decreased blood pressure with an ED₃₀ of 0.27 mg/kg and a duration of action of greater than 24 h in renal hypertensive rats. XR510 is also active in furosemide-treated dogs following iv and po administration. The pharmacological properties of such a balanced angiotensin II receptor antagonist are currently under investigation.

Experimental Section

Angiotensin II Receptor Binding Assays. The binding to the AT₁ or AT₂ receptor subtypes was determined using rat isolated adrenal membrane homogenates in the presence of 10⁻⁶ M PD123177 or 10⁻⁶ M losartan, respectively. Procedures for the preparation of the adrenal membrane homogenates and details of the binding assays are described in the literature.^{5,17} [¹²⁵I][Sar¹,Ile⁸]Ang II was adopted as the radioligand for the present. The intraassay variability is 5%, and the interassay variability is 20%. All compounds were tested in duplicate studies and were compared with DuP 753 and saralasin as internal standards.

In Vivo Assay. The antihypertensive effect was determined in conscious renal artery-ligated hypertensive rats. The experimental details and methodology of the *in vivo* assay are described in ref 19.

Physical Methods. Melting points were determined in an open capillary with a Thomas-Hoover melting point apparatus and are uncorrected. IR spectra were determined with a Perkin-Elmer 1600 series FTIR. NMR spectra were determined with a Varian VXR-300a. Microanalyses were performed by Quantitative Technologies Inc. and were within $\leq 0.4\%$ of the calculated values. Mass spectra were obtained on a HP 5988A MS/HP Partial Bean Interface. Chromatography was done using EM Science silica gel 60. Radiolabeled [¹²⁵I]Ang II was obtained from Du Pont NEN Products (Boston, MA).

1-(4-Bromo-2-fluorobenzyl)-4-ethyl-5-formyl-2-propyl-1H-imidazole (14). A solution of 4-bromo-2-fluorotoluene (**12**) (18.9 g, 0.10 mol), *N*-bromosuccinamide (21.4 g, 0.12 mol), and azobisisobutyronitrile (1.70 g, 0.01 mol) in CCl₄ (150 mL) was refluxed under N₂ for 4 h. The mixture was cooled, and the solid was filtered off and washed with CCl₄. The filtrate was washed with water and brine, dried over MgSO₄, and concentrated to a yellow oil (29 g). This material was used without further purification in the next step.

4-Ethyl-5-formyl-2-propyl-1H-imidazole (**13**)¹⁵ (16.6 g, 0.10 mol), potassium carbonate (41.5 g, 0.30 mol), and 4-bromo-2-fluorobenzyl bromide obtained from above (26.8 g, 0.10 mol) were added together with 150 mL of DMF. The reaction mixture was stirred at room temperature for 12 h under N₂. The mixture was poured into water and extracted with EtOAc. The combined organic mixture was washed with H₂O and brine, dried over MgSO₄, and concentrated. The crude product mixture was purified by flash chromatography (silica gel, 30–50% EtOAc/hexane) to yield 21.9 g of a light yellow solid (62%). ¹H NMR (CDCl₃): δ 0.95 (t, 3H, CH₃), 1.32 (t, 3H, CH₃), 1.70 (m, 2H, CH₂), 2.60 (m, 2H, CH₂), 2.85 (q, 2H, CH₂), 5.52 (s, 2H, ArCH₂), 6.60 (t, 1H, ArH), 7.18 (d, 1H, ArH), 7.25 (d, 1H, ArH), 9.75 (s, 1H, CHO).

1-[[2'-[(*tert*-Butylamino)sulfonyl]-3-fluoro(1,1'-biphenyl)-4-yl]methyl]-4-ethyl-5-formyl-2-propyl-1*H*-imidazole (16). 1-(4-Bromo-2-fluorobenzyl)-4-ethyl-5-formyl-2-propyl-1*H*-imidazole (14) (10.6 g, 0.03 mol), [2'-[(*tert*-butylamino)sulfonyl]phenyl]boronic acid (15)¹⁹ (9.3 g, 0.036 mol), sodium carbonate (30 mL of 2 M aqueous solution), and tetrabutylammonium bromide (1.2 g, 3.6 mmol) were added together with 225 mL of toluene. Tetrakis(triphenylphosphine)palladium(0) (1.73 g, 1.5 mmol) was added. The mixture was refluxed under N₂ for 20 h. The solvent was removed *in vacuo*, and the residue was partitioned between H₂O and CH₂Cl₂. The aqueous layer was extracted with CH₂Cl₂, and the combined organic solution was washed with brine, dried over MgSO₄, and concentrated. The crude product was purified by flash column chromatography (silica gel, 25% EtOAc/hexane) to give 12.6 g of the desired product (86%). MS: 486 (M + H). ¹H NMR (CDCl₃): δ 0.99 (t, 3H, CH₃), 1.01 (s, 9H, CH₃), 1.36 (t, 3H, CH₃), 1.73 (m, 2H, CH₂), 2.67 (m, 2H, CH₂), 2.90 (q, 2H, CH₂), 3.57 (s, 1H, NH), 5.62 (s, 2H, ArCH₂), 6.78 (t, 1H, ArH), 7.19 (d, 1H, ArH), 7.29 (m, 2H, ArH), 7.54 (m, 2H, ArH), 8.17 (d, 1H, ArH), 9.77 (s, 1H, CHO).

1-[[2'-[(*tert*-Butylamino)sulfonyl]-3-fluoro(1,1'-biphenyl)-4-yl]methyl]-4-ethyl-5-propenoyl-2-propyl-1*H*-imidazole (17). To a solution of 1-[[2'-[(*tert*-butylamino)sulfonyl]-3-fluoro(1,1'-biphenyl)-4-yl]methyl]-4-ethyl-5-formyl-2-propyl-1*H*-imidazole (16) (2.25 g, 4.63 mmol) in THF (10 mL) was added vinylmagnesium bromide (14.8 mL of 1.0 M solution in THF) over 20 min. The reaction mixture was stirred at room temperature under N₂ for 1.5 h. It was then quenched with 1 N aqueous HCl. After the THF was removed, the mixture was extracted with CH₂Cl₂. The organic solution was washed with H₂O and brine, dried over MgSO₄, and concentrated to an orange oil. The resulting oil was dissolved in 40 mL of CH₂Cl₂, and manganese(IV) oxide (8.0 g) was added. The resulting mixture was stirred at room temperature under N₂ for 24 h. The mixture was filtered through Celite and washed with CH₂Cl₂. The filtrate was concentrated and chromatographed on silica gel with 25% ethyl acetate in hexane to yield 1.48 g of a yellow oil (62%). MS: 558 (M + H). ¹H NMR (CDCl₃): δ 0.98 (t, 3H, CH₃), 0.99 (s, 9H, CH₃), 1.24 (t, 3H, CH₃), 1.77 (m, 2H, CH₂), 2.63 (m, 2H, CH₂), 2.90 (q, 2H, CH₂), 3.50 (s, 1H, NH), 5.59 (s, 2H, ArCH₂), 5.79 (d, 1H, CH), 6.31 (d, 1H, CH), 6.71 (t, 1H, ArH), 6.95 (m, 2H, CH₂=), 7.18 (d, 1H, ArH), 7.30 (m, 2H, ArH), 7.52 (m, 2H, ArH), 8.17 (d, 1H, ArH).

1-(4-Bromo-2-fluorobenzyl)-4-ethyl-5-propenoyl-2-propyl-1*H*-imidazole (19). To a solution of 1-(4-bromo-2-fluorobenzyl)-4-ethyl-5-formyl-2-propyl-1*H*-imidazole (14) (21.58 g, 61.1 mmol) in THF (150 mL) was added vinylmagnesium bromide (92.0 mL of 1.0 M solution in THF, 92.0 mmol) over 30 min. The reaction mixture was stirred at room temperature under N₂ for 1 h. It was then quenched with 100 mL of 1 N aqueous HCl. The mixture was extracted with CH₂Cl₂, and the organic solution was washed with H₂O and brine, dried over MgSO₄, and concentrated to an orange oil. The resulting oil was dissolved in CH₂Cl₂ and manganese(IV) oxide (79.97 g, 920 mmol) was added. The resulting mixture was stirred at room temperature under N₂ overnight. The mixture was filtered through Celite and washed with CH₂Cl₂. The filtrate was concentrated and chromatographed on silica gel with 1/1 ethyl acetate/hexane to yield 20.4 g of a yellow oil (88%). ¹H NMR (CDCl₃): δ 0.95 (t, 3H, CH₃), 1.30 (t, 3H, CH₃), 1.70 (m, 2H, CH₂), 2.60 (m, 2H, CH₂), 2.88 (q, 2H, CH₂), 5.48 (s, 2H, ArCH₂), 5.80 (d, 1H, CH=), 6.30 and 6.62 (d, 2H, =CH₂), 6.90 (t, 1H, ArH), 7.15 (d, 1H, ArH), 7.25 (d, 1H, ArH).

1-(4-Bromo-2-fluorobenzyl)-5-[3-(*N*-pyridin-3-ylbutanamido)propanoyl]-4-ethyl-2-propyl-1*H*-imidazole (20). To a solution of 1-(4-bromo-2-fluorobenzyl)-4-ethyl-5-propenoyl-2-propyl-1*H*-imidazole (19) (3.36 g, 8.86 mmol) and triethylamine (2.50 mL) in THF (150 mL) was added 3-aminopyridine (1.66 mL, 17.64 mmol). The mixture was refluxed under N₂ for 48 h. The solvent was removed *in vacuo*. The residue was dissolved in EtOAc and washed with H₂O and brine. The organic solution was then dried over MgSO₄ and concentrated. The crude mixture was chromatographed on silica gel with 5% MeOH/CH₂Cl₂ to yield 2.31 g of a yellow solid. The above solid was dissolved in THF (50 mL), and triethylamine (1.4

mL, 9.76 mmol) and butyryl chloride (1.0 mL, 9.76 mmol) were then added. The mixture was refluxed under N₂ for 3 h. The solvent was removed *in vacuo*. The residue was dissolved in EtOAc and washed with H₂O, 1 N NaOH, and brine. The organic solution was then dried over MgSO₄, concentrated, and chromatographed on silica gel with 5% MeOH/CH₂Cl₂ (1.83 g, 38% yield). MS: 543 [M + H]. ¹H NMR (CDCl₃): δ 0.79 (t, 3H, CH₃), 0.94 (t, 3H, CH₃), 1.31 (t, 3H, CH₃), 1.48–1.73 (m, 4H, CH₂), 1.94 (t, 2H, CH₂), 2.53 (t, 2H, CH₂), 2.90 (q, 2H, CH₂), 3.08 (t, 2H, CH₂), 3.97 (t, 2H, CH₂), 5.38 (s, 2H, ArCH₂), 6.37 (t, 1H, ArH), 7.12 (d, 1H, ArH), 7.23 (m, 1H, ArH), 7.32 (m, 1H, ArH), 7.43 (m, 1H, ArH), 8.39 (s, 1H, ArH), 8.58 (d, 1H, ArH).

1-[[2'-[(*tert*-Butylamino)sulfonyl]-3-fluoro(1,1'-biphenyl)-4-yl]methyl]-5-[3-(*N*-pyridin-3-ylbutanamido)propanoyl]-4-ethyl-2-propyl-1*H*-imidazole (18). **Method A.** To a solution of 1-[[2'-[(*tert*-butylamino)sulfonyl]-3-fluoro(1,1'-biphenyl)-4-yl]methyl]-4-ethyl-5-propenoyl-2-propyl-1*H*-imidazole (17) (6.9 g, 13.5 mmol) and triethylamine (3 mL) in THF (250 mL) was added 3-aminopyridine (1.91 g, 20.25 mmol). The mixture was refluxed under N₂ for 12 h. TLC (4/6 hexane/ethyl acetate) still showed starting material. Half an equivalent of 3-aminopyridine (0.64 g) and Et₃N were added, and the mixture was refluxed for 5 h. The solvent was removed *in vacuo*. The residue was dissolved in EtOAc and washed with H₂O and brine. The organic solution was then dried over MgSO₄ and concentrated to a brown oil. The crude product mixture was dissolved in 1-chlorobutane and washed with pH 4 buffer to remove some of the impurities. The organic mixture was dried over MgSO₄ and concentrated to a tan solid (7.6 g). The above solid was dissolved in THF (125 mL), and triethylamine (1.9 mL) and butyryl chloride (1.4 mL, 13.18 mmol) were added. The mixture was refluxed under N₂ for 4 h. One more equivalent of butyryl chloride (1.4 mL) and triethylamine (1.9 mL) were added. The reaction mixture was refluxed for a total of 12 h. The solvent was removed *in vacuo*. The residue was dissolved in EtOAc and washed with H₂O, 1 N NaOH, and brine. The organic solution was then dried over MgSO₄ and concentrated to a yellow oil. The compound was purified by flash column chromatography (silica gel, 10% hexane in ethyl acetate) to give 6.0 g of the desired product (66% yield).

Method B. 1-(4-Bromo-2-fluorobenzyl)-5-[3-(*N*-pyridin-3-ylbutanamido)propanoyl]-4-ethyl-2-propyl-1*H*-imidazole (20) (1.83 g, 3.37 mmol), [2'-[(*tert*-butylamino)sulfonyl]phenyl]boronic acid (15) (1.04 g, 4.04 mmol), sodium carbonate (10 mL of 2 M aqueous solution), and tetrabutylammonium bromide (54 mg, 5%) were added together with 50 mL of toluene. Tetrakis(triphenylphosphine)palladium(0) (0.19 g, 5%) was added. The mixture was refluxed under N₂ for 4.5 h. The solvent was removed *in vacuo*, and the residue was partitioned between H₂O and CH₂Cl₂. The aqueous layer was extracted with CH₂Cl₂, and the combined organic solution was washed with brine, dried over MgSO₄, and concentrated. The crude product was purified by flash column chromatography (silica gel, 5% MeOH/CH₂Cl₂) to give 1.15 g of pale yellow foam (50%). MS: 677 (M + H). ¹H NMR (CDCl₃): δ 0.81 (t, 3H, CH₃), 0.96 (t, 3H, CH₃), 0.99 (s, 9H, CH₃), 1.32 (t, 3H, CH₃), 1.57 (m, 2H, CH₂), 1.68 (m, 2H, CH₂), 1.95 (t, 2H, CH₂), 2.58 (t, 2H, CH₂), 2.88 (q, 2H, CH₂), 3.08 (t, 2H, CH₂), 3.96 (s, 1H, NH), 3.98 (t, 2H, CH₂), 5.48 (s, 2H, ArCH₂), 6.52 (t, 1H, ArH), 7.12 (d, 1H, ArH), 7.22 (m, 2H, ArH), 7.37 (m, 1H, ArH), 7.50 (m, 3H, ArH), 8.15 (d, 1H, ArH), 8.32 (s, 1H, ArH), 8.57 (d, 1H, ArH).

1-[[2'-[[Isopentoxycarbonyl]amino]sulfonyl]-3-fluoro(1,1'-biphenyl)-4-yl]methyl]-5-[3-(*N*-pyridin-3-ylbutanamido)propanoyl]-4-ethyl-2-propyl-1*H*-imidazole (34) and Its Potassium Salt (1, XR510). 1-[[2'-[(*tert*-Butylamino)sulfonyl]-3-fluoro(1,1'-biphenyl)-4-yl]methyl]-5-[3-(*N*-pyridin-3-ylbutanamido)propanoyl]-4-ethyl-2-propyl-1*H*-imidazole (18) (6.0 g, 8.88 mmol) was stirred with 100 mL of trifluoroacetic acid under N₂ for 12 h. The solvent was removed *in vacuo*. The residue was dissolved in CH₂Cl₂ and washed with aqueous NaHCO₃ and brine. The organic solution was filtered through phase separator paper and then concentrated to a light yellow foam (4.6 g). The above solid was dissolved in CH₂Cl₂ (100 mL). To the solution was added 4-(dimethylamino)pyridine

(1.0 g, 8.2 mmol) and pyridine (10 mL), followed by isoamyl chloroformate (3.34 g, 22.2 mmol). The mixture was stirred at room temperature under N₂ for 56 h. The reaction mixture was diluted with CH₂Cl₂ and washed with 10% of aqueous citric acid and brine. It was dried over MgSO₄ and concentrated. The crude product mixture was purified by flash column chromatography (silica gel, 5% MeOH in CH₂Cl₂) to give 4.6 g of compound **34** (71% yield). MS: 735 [M + H]. ¹H NMR (CDCl₃): δ 0.77 (t, 3H, CH₃), 0.85 (d, 6H, CH₃), 0.94 (t, 3H, CH₃), 1.34 (t, 3H, CH₃), 1.38–1.60 (m, 5H, CH and CH₂), 1.70 (m, 2H, CH₂), 1.95 (t, 2H, CH₂), 2.52 (t, 2H, CH₂), 2.93 (q, 2H, CH₂), 3.21 (br s, 2H, CH₂), 4.08 (t, 4H, CH₂), 5.50 (br s, 2H, CH₂Ar), 6.19 (t, 1H, ArH), 7.03 (dd, 1H, ArH), 7.09 (dd, 3H, ArH), 7.22 (dd, 1H, ArH), 7.42 (m, 1H, ArH), 7.53–7.68 (m, 3H, ArH), 7.71 (d, 1H, ArH), 8.31 (dd, 1H, ArH), 8.44 (dd, 1H, ArH). Anal. (C₃₉H₄₈FN₅O₆S) C, H, N.

Compound **34** (0.67 g) was dissolved in 50 mL of MeOH and 5 mL of H₂O. The mixture was titrated with 0.09 M of aqueous KOH until pH ~7.5 (8.7 mL). The solvent was removed *in vacuo*, and the residue was dissolved in CHCl₃/CH₃OH and then precipitated with hexane to give 0.58 g of off-white solid (1, XR510). ¹H NMR (CDCl₃): δ 0.69 (t, 3H, CH₃), 0.70 (d, 6H, CH₃), 0.90 (t, 3H, CH₃), 1.19 (m, 5H, CH₂ and CH₃), 1.44 (m, 3H, CH and CH₂), 1.64 (m, 2H, CH₂), 1.85 (t, 2H, CH₂), 2.54 (t, 2H, CH₂), 2.74 (q, 2H, CH₂), 2.90 (t, 2H, CH₂), 3.70 (t, 2H, CH₂), 4.03 (t, 2H, CH₂), 5.24 (s, 2H, CH₂Ar), 6.31 (t, 1H, ArH), 6.90 (dd, 1H, ArH), 7.05 (dd, 1H, ArH), 7.14 (d, 1H, ArH), 7.32 (m, 2H, ArH), 7.58 (d, 1H, ArH), 8.01 (d, 1H, ArH), 8.29 (d, 1H, ArH), 8.52 (d, 1H, ArH). Anal. (C₃₉H₄₇FN₅O₆SK) C, H, N.

The following compounds were prepared by the same methods described above for the synthesis of 11 and XR510 using appropriate starting materials.

1-[[2'-[[(*n*-Butoxycarbonyl)amino]sulfonyl]-3-fluoro-(1,1'-biphenyl)-4-yl)methyl]-5-[3-(*N*-propylbutanamido)propanoyl]-4-ethyl-2-propyl-1*H*-imidazole (**24**). MS: 685 [M + H]. ¹H NMR (DMSO-*d*₆): δ 0.72–0.98 (m, 12H, CH₃), 1.312–1.57 (m, 10H, CH, CH₂, CH₃), 1.59–1.66 (m, 2H, CH₂), 2.17–2.30 (m, 2H, CH₂), 2.58 (m, 2H, CH₂), 2.80–3.22 (m, 6H, CH₂), 3.40–3.61 (m, 6H, CH₂), 5.58 (s, 2H, CH₂Ar), 6.42 (m, 1H, ArH), 7.09 (m, 2H, ArH), 7.38 (m, 2H, ArH), 7.96 (m, 1H, ArH). Anal. (C₃₆H₄₉FN₄O₆S·1.5H₂O) C, H, N.

1-[[2'-[[(*n*-Butoxycarbonyl)amino]sulfonyl]-3-fluoro-(1,1'-biphenyl)-4-yl)methyl]-5-[3-(*N*-propylbenzamido)propanoyl]-4-ethyl-2-propyl-1*H*-imidazole (**25**). MS: 719 [M + H]. ¹H NMR (CDCl₃): δ 0.72–1.82 (m, 20H, CH₂, CH₃), 2.53–3.42 (m, 8H, CH₂), 3.70 (m, 2H, CH₂), 3.95 (t, 2H, CH₂), 5.58 (s, 2H, CH₂Ar), 6.61 (m, 1H, ArH), 7.04 (m, 2H, ArH), 7.21–7.40 (m, 6H, ArH), 7.52–7.65 (m, 2H, ArH), 8.36 (d, 1H, ArH). Anal. (C₃₉H₄₇FN₄O₆S) C, H, N.

1-[[2'-[[(*n*-Butoxycarbonyl)amino]sulfonyl]-3-fluoro-(1,1'-biphenyl)-4-yl)methyl]-5-[3-(*N*-butylbenzamido)propanoyl]-4-ethyl-2-propyl-1*H*-imidazole (**26**). MS: 733 [M + H]. ¹H NMR (CDCl₃): δ 0.72–1.02 (m, 9H, CH₃), 1.12–1.61 (m, 11H, CH₂, CH₃), 1.74 (m, 2H, CH₂), 2.75 (t, 2H, CH₂), 2.86–3.76 (m, 6H, CH₂), 3.72 (t, 2H, CH₂), 3.96 (t, 2H, CH₂), 5.58 (s, 2H, CH₂Ar), 6.60 (br s, 1H, ArH), 7.04 (m, 2H, ArH), 7.25–7.72 (m, 8H, ArH), 8.26 (d, 1H, ArH).

1-[[2'-[[(*n*-Butoxycarbonyl)amino]sulfonyl]-3-fluoro-(1,1'-biphenyl)-4-yl)methyl]-5-[3-(*N*-phenylbenzamido)propanoyl]-4-ethyl-2-propyl-1*H*-imidazole (**27**). MS: 753 [M + H]. ¹H NMR (CDCl₃): δ 0.85 (t, 3H, CH₃), 0.98 (t, 3H, CH₃), 1.20 (m, 2H, CH₃), 1.27 (t, 2H, CH₂), 1.42 (m, 2H, CH₂), 1.75 (m, 2H, CH₂), 2.65 (t, 2H, CH₂), 2.85 (q, 2H, CH₂), 3.15 (t, 2H, CH₂), 3.95 (t, 2H, CH₂), 4.20 (t, 2H, CH₂), 5.50 (s, 2H, CH₂Ar), 6.60 (t, 1H, ArH), 7.02 (d, 4H, ArH), 7.15 (m, 4H, ArH), 7.20 (d, 2H, ArH), 7.30 (t, 3H, ArH), 7.58 (m, 2H, ArH), 8.25 (d, 1H, ArH). Anal. for K salt (C₄₂H₄₄FN₄O₆SK·2H₂O) C, H, N.

1-[[2'-[[(*n*-Butoxycarbonyl)amino]sulfonyl]-3-fluoro-(1,1'-biphenyl)-4-yl)methyl]-5-[3-(*N*-phenylbutanamido)propanoyl]-4-ethyl-2-propyl-1*H*-imidazole (**28**). MS: 719 [M + H]. ¹H NMR (CDCl₃): δ 0.80 (t, 3H, CH₃), 0.85 (t, 3H, CH₃), 0.99 (t, 3H, CH₃), 1.20 (m, 2H, CH₃), 1.26 (t, 2H, CH₂), 1.47 (m, 2H, CH₂), 1.58 (m, 2H, CH₂), 1.75 (m, 2H, CH₂), 2.01 (t, 2H, CH₂), 2.66 (t, 2H, CH₂), 2.84 (q, 2H, CH₂), 3.01 (t, 2H,

CH₂), 3.91 (t, 2H, CH₂), 4.00 (t, 2H, CH₂), 5.50 (s, 2H, CH₂Ar), 6.55 (t, 1H, ArH), 7.05 (t, 2H, ArH), 7.09 (d, 2H, ArH), 7.28 (d, 1H, ArH), 7.40 (m, 3H, ArH), 7.60 (m, 2H, ArH), 8.30 (d, 1H, ArH). Anal. for K salt (C₃₉H₄₆FN₄O₆SK) C, H, N.

1-[[2'-[[(*Isopentoxycarbonyl*)amino]sulfonyl]-3-fluoro-(1,1'-biphenyl)-4-yl)methyl]-5-[3-(*N*-phenylbenzamido)propanoyl]-4-ethyl-2-propyl-1*H*-imidazole (**29**). MS: 768 [M + H]. ¹H NMR (CDCl₃): δ 0.77 (d, 6H, CH₃), 0.97 (t, 3H, CH₃), 1.20 (t, 3H, CH₃), 1.31 (m, 2H, CH₂), 1.48 (m, 1H, CH), 1.70 (m, 2H, CH₂), 2.59 (t, 2H, CH₂), 2.77 (q, 2H, CH₂), 3.06 (t, 2H, CH₂), 3.79 (t, 2H, CH₂), 4.29 (t, 2H, CH₂), 5.24 (s, 2H, CH₂Ar), 6.40 (t, 1H, ArH), 6.97 (d, 3H, ArH), 7.02 (m, 2H, ArH), 7.07–7.25 (m, 9H, ArH), 7.37 (m, 2H, ArH), 8.16 (d, 1H, ArH). Anal. (C₄₃H₄₇FN₄O₆S) C, H, N.

1-[[2'-[[(*Isopentoxycarbonyl*)amino]sulfonyl]-3-fluoro-(1,1'-biphenyl)-4-yl)methyl]-5-[3-(*N*-phenylpyridine-4-carboxamido)propanoyl]-4-ethyl-2-propyl-1*H*-imidazole (**30**). MS: 768 [M + H]. ¹H NMR (CDCl₃): δ 0.81 (d, 6H, CH₃), 0.96 (t, 3H, CH₃), 1.20–1.48 (m, 6H, CH, CH₂, CH₃), 1.70 (m, 2H, CH₂), 2.61 (t, 2H, CH₂), 2.83 (q, 2H, CH₂), 3.09 (t, 2H, CH₂), 3.98 (t, 2H, CH₂), 4.19 (t, 2H, CH₂), 5.47 (s, 2H, CH₂Ar), 6.55 (t, 1H, ArH), 6.99–7.29 (m, 10H, ArH), 7.58 (m, 2H, ArH), 8.26 (d, 1H, ArH), 8.40 (d, 2H, ArH). Anal. (C₄₂H₄₆FN₅O₆S) C, H, N.

1-[[2'-[[(*Isopentoxycarbonyl*)amino]sulfonyl]-3-fluoro-(1,1'-biphenyl)-4-yl)methyl]-5-[3-(*N*-pyridin-3-ylpyridine-4-carboxamido)propanoyl]-4-ethyl-2-propyl-1*H*-imidazole (**31**). MS: 769 [M + H]. ¹H NMR (CDCl₃): δ 0.83 (d, 6H, CH₃), 0.95 (t, 3H, CH₃), 1.19–1.32 (m, 4H, CH, CH₂), 1.70 (m, 2H, CH₂), 2.52 (t, 2H, CH₂), 2.95 (q, 2H, CH₂), 3.32 (br s, 2H, CH₂), 4.01 (t, 2H, CH₂), 4.34 (br s, 2H, CH₂), 5.40 (br s, 2H, CH₂Ar), 6.15 (t, 1H, ArH), 6.95 (d, 1H, ArH), 7.00–7.72 (m, 9H, ArH), 8.31 (m, 2H, ArH), 8.46 (d, 2H, ArH). Anal. for K salt (C₄₁H₄₄FN₆O₆SK·¹/₂H₂O) C, H, N.

1-[[2'-[[(*Isopentoxycarbonyl*)amino]sulfonyl]-3-fluoro-(1,1'-biphenyl)-4-yl)methyl]-5-[3-(*N*-pyridin-3-ylpyridine-3-carboxamido)propanoyl]-4-ethyl-2-propyl-1*H*-imidazole (**32**). MS: 769 [M + H]. ¹H NMR (CDCl₃): δ 0.86 (d, 6H, CH₃), 0.97 (t, 3H, CH₃), 1.38 (t, 3H, CH₃), 1.38 (m, 2H, CH₂), 1.50 (m, 1H, CH), 1.72 (m, 2H, CH₂), 2.52 (t, 2H, CH₂), 2.98 (q, 2H, CH₂), 3.34 (br s, 2H, CH₂), 4.00 (t, 2H, CH₂), 4.38 (br s, 2H, CH₂), 5.40 (br s, 2H, CH₂Ar), 6.10 (t, 1H, ArH), 6.92 (d, 3H, ArH), 7.03–7.20 (m, 3H, ArH), 7.38 (dd, 2H, ArH), 7.48–7.61 (m, 4H, ArH), 7.78 (d, 1H, ArH), 8.28 (m, 2H, ArH), 8.33 (s, 1H, ArH), 8.45 (d, 1H, ArH). Anal. (C₄₁H₄₅FN₆O₆S) C, H, N.

1-[[2'-[[(*Isopentoxycarbonyl*)amino]sulfonyl]-3-fluoro-(1,1'-biphenyl)-4-yl)methyl]-5-[3-(*N*-pyridin-2-ylpyridine-3-carboxamido)propanoyl]-4-ethyl-2-propyl-1*H*-imidazole (**33**). MS: 770 [M + H]. ¹H NMR (CDCl₃): δ 0.75 (d, 6H, CH₃), 0.87 (t, 3H, CH₃), 0.93 (t, 3H, CH₃), 1.26 (m, 2H, CH₂), 1.47 (m, 1H, CH), 1.68 (m, 2H, CH₂), 2.58 (t, 2H, CH₂), 2.84 (q, 2H, CH₂), 3.24 (t, 2H, CH₂), 3.77 (t, 2H, CH₂), 4.38 (t, 2H, CH₂), 5.28 (br s, 2H, CH₂Ar), 6.40 (t, 1H, ArH), 6.90 (d, 1H, ArH), 7.00 (m, 2H, ArH), 7.09 (m, 2H, ArH), 7.18 (m, 1H, ArH), 7.35 (m, 2H, ArH), 7.48 (m, 1H, ArH), 7.67 (d, 1H, ArH), 8.06 (t, 1H, ArH), 8.32 (s, 1H, ArH), 8.35 (d, 1H, ArH), 8.44 (d, 1H, ArH). Anal. for K salt (C₄₁H₄₅FN₆O₆SK·2H₂O) C, H, N.

1-[[2'-[[(*Isopentoxycarbonyl*)amino]sulfonyl]-3-fluoro-(1,1'-biphenyl)-4-yl)methyl]-5-[3-(*N*-pyridin-3-ylisobutanamido)propanoyl]-4-ethyl-2-propyl-1*H*-imidazole (**35**). MS: 763 [M + H]. ¹H NMR (CDCl₃): δ 0.84 (d, 6H, CH₃), 0.93 (m, 9H, CH₃), 1.33 (t, 3H, CH₃), 1.42 (t, 2H, CH), 1.47 (m, 1H, CH), 1.68 (m, 2H, CH₂), 2.34 (m, 2H, CH), 2.52 (t, 2H, CH₂), 2.95 (q, 2H, CH₂), 3.20 (br s, 2H, CH₂), 4.07 (t, 4H, CH₂), 5.28 (br s, 2H, CH₂Ar), 6.18 (t, 1H, ArH), 7.03 (d, 1H, ArH), 7.09 (d, 1H, ArH), 7.42 (m, 1H, ArH), 7.57 (m, 2H, ArH), 7.63 (m, 1H, ArH), 7.74 (s, 1H, ArH), 8.30 (d, 1H, ArH), 8.45 (d, 1H, ArH). Anal. for K salt (C₃₉H₄₈FN₅O₆SK·H₂O) C, H, N.

1-[[2'-[[(*Isopentoxycarbonyl*)amino]sulfonyl]-3-fluoro-(1,1'-biphenyl)-4-yl)methyl]-5-[3-(*N*-pyridin-3-ylpropanamido)propanoyl]-4-ethyl-2-propyl-1*H*-imidazole (**36**). MS: 720 [M + H]. ¹H NMR (CDCl₃): δ 0.83 (d, 6H, CH₃), 0.95 (t, 3H, CH₃), 1.33 (t, 3H, CH₃), 1.42 (m, 3H, CH and CH₂), 1.70 (m, 2H, CH₂), 1.97 (t, 2H, CH₂), 2.52 (t, 2H, CH₂), 2.91 (q, 2H,

CH₂), 3.10 (br s, 2H, CH₂), 4.08 (t, 4H, CH₂), 5.41 (br s, 2H, CH₂Ar), 6.19 (t, 1H, ArH), 7.03 (dd, 2H, ArH), 7.20 (d, 1H, ArH), 7.40 (m, 1H, ArH), 7.50–7.67 (m, 3H, ArH), 7.70 (s, 1H, ArH), 8.29 (d, 1H, ArH), 8.41 (d, 1H, ArH). Anal. (C₃₈H₄₆FN₅O₆S) C, H, N.

1-[[2'-[[Isopentoxycarbonyl]amino]sulfonyl]-3-fluoro-(1,1'-biphenyl)-4-yl]methyl]-5-[3-(N-pyridin-3-ylethanimido)propanoyl]-4-ethyl-2-propyl-1H-imidazole (37). MS: 706 [M + H]. ¹H NMR (CDCl₃): δ 0.90 (d, 6H, CH₃), 0.92 (t, 3H, CH₃), 1.22 (t, 3H, CH₃), 1.38 (m, 2H, CH₂), 1.55 (m, 3H, CH, CH₂), 2.30 (t, 2H, CH₂), 2.46 (br s, 3H, CH₃), 2.80 (q, 2H, CH₂), 3.18 (m, 2H, CH₂), 4.02 (t, 2H, CH₂), 4.18 (t, 2H, CH₂), 5.18 (s, 2H, CH₂Ar), 6.03 (t, 1H, ArH), 6.78 (m, 2H, ArH), 6.92 (d, 1H, ArH), 7.08 (d, 1H, ArH), 7.18 (m, 1H, ArH), 7.24 (d, 1H, ArH), 7.55 (m, 2H, ArH), 8.31 (d, 1H, ArH).

1-[[2'-[[Isopentoxycarbonyl]amino]sulfonyl](1,1'-biphenyl)-4-yl]methyl]-5-[3-(N-pyridin-3-ylbutanamido)propanoyl]-4-ethyl-2-propyl-1H-imidazole (38). MS: 716 [M + H]. ¹H NMR (CDCl₃): δ 0.76 (t, 3H, CH₃), 0.85 (d, 6H, CH₃), 0.93 (t, 3H, CH₃), 1.35 (t, 3H, CH₃), 1.42 (m, 2H, CH₂), 1.46 (m, 1H, CH), 1.50 (m, 2H, CH₂), 1.70 (m, 2H, CH₂), 1.92 (t, 2H, CH₂), 2.65 (t, 2H, CH₂), 2.97 (q, 2H, CH₂), 3.24 (m, 2H, CH₂), 4.07 (m, 4H, CH₂), 5.48 (br s, 2H, CH₂Ar), 6.72 (d, 2H, ArH), 7.23 (t, 2H, ArH), 7.30 (d, 2H, ArH), 7.41 (m, 1H, ArH), 7.59 (m, 2H, ArH), 7.68 (s, 1H, ArH), 8.32 (d, 1H, ArH), 8.45 (d, 1H, ArH). Anal. for K salt (C₃₉H₄₈FN₅O₆SK·KOH) C, H, N.

1-[[2'-[[Isopentoxycarbonyl]amino]sulfonyl](1,1'-biphenyl)-4-yl]methyl]-5-[3-(N-pyridin-3-ylpyridine-3-carboxamido)propanoyl]-4-ethyl-2-propyl-1H-imidazole (39). MS: 751 [M + H]. ¹H NMR (CDCl₃): δ 0.83 (d, 6H, CH₃), 0.87 (t, 3H, CH₃), 1.25 (t, 3H, CH₃), 1.35 (m, 3H, CH₂, CH), 1.70 (m, 2H, CH₂), 2.52 (t, 2H, CH₂), 2.95 (q, 2H, CH₂), 3.32 (t, 2H, CH₂), 3.99 (t, 2H, CH₂), 4.34 (t, 2H, CH₂), 5.39 (s, 2H, CH₂Ar), 6.30 (d, 2H, ArH), 7.10–7.22 (m, 4H, ArH), 7.33 (m, 1H, ArH), 7.50 (m, 3H, ArH), 7.68 (d, 1H, ArH), 8.26 (d, 2H, ArH), 8.32 (t, 1H, ArH), 8.44 (d, 1H, ArH). Anal. for K salt (C₄₁H₄₅FN₆O₆SK·H₂O) C, H, N.

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