Balanced AT_1/AT_2 Receptor Antagonists. 4.[1,2] XR510 and Related 5-(3-Amidopropanoyl)imidazoles Possessing Equal Affinity for the AT_1 and AT_2 Receptors

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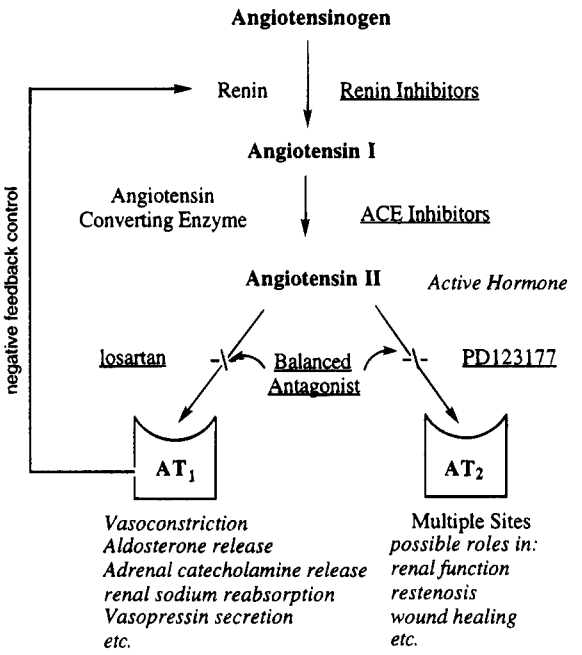
The identification of the AT_1 and AT_2 receptor subtypes has stimulated interest in developing balanced angiotensin II receptor antagonists. A series of 5-(3-amidopropanoyl)imidazoles has been prepared which possess balanced affinity for the AT_1 and AT_2 receptors. XR510 (**1**), 1-[[2′-[[(isopentoxycarbonyl)amino]sulfonyl]-3-fluoro(1,1′-biphenyl)-4-yl]methyl]-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 AT_1 and AT_2. The AT_1 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 AT_1-selective Ang II antagonists such as Cozaar (**2**, losartan, DuP 753, see Figure 1).[6] The physiological functions of the AT_2 receptor are not clearly defined at this time, but AT_2 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 AT_2-selective receptor antagonists such as PD123177 (**3**).[11] It has been reported that blockade of the AT_1 receptor by losartan in animals and humans increased plasma levels of renin and Ang II.[12] This may act on the unblocked AT_2 receptors, although no unexpected effects attributable to AT_2 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 AT_2 blockade, we sought a nonpeptide antagonist with an IC_{50} less than 10 nM for AT_1 and an AT_2/AT_1 ratio close to one.

Recently some compounds with affinity for both the AT_1 and AT_2 receptors have been described.[14] The quinazolinone biphenyl tetrazole L-159,689 (**4**)[14c] reported by the Merck research group has an IC_{50} of 1.0 nM for the AT_1 receptor and 0.7 nM for the AT_2 receptor. The quinazolinone biphenyl sulfonylcarbamate L-162,-393 (**5**)[14d] showed similar affinity. Merck has also reported a class of potent and balanced imidazopyridines such as L-162,620 (**6**)[14b] with subnanomolar affinity for both receptors and an AT_2/AT_1 ratio of 2.8.

Scheme 1. Renin–Angiotensin Cascade



Our approach to balanced AT_1/AT_2 receptor antagonists was to build AT_2 affinity by structural modifications of our AT_1-selective biphenylylimidazoles. The evolution of our AT_1-selective antagonists into balanced antagonists is illustrated in Scheme 2. Biphenyl "ortho" substitution on the inner phenyl ring of the AT_1-selective DMP 581 (**7**)[15] provided compounds such as **8**[1a] with micromolar AT_2 affinity. When Merck scientists discovered that using certain acyl sulfonamides and sulfonylcarbamates as tetrazole replacements could increase AT_2 affinity,[14] we combined "ortho" substitution with a sulfonylcarbamate as the acid isostere in the imidazole series and further improved AT_2 affinity 20–1000-fold (**9**).[1a] Modification of the R^5 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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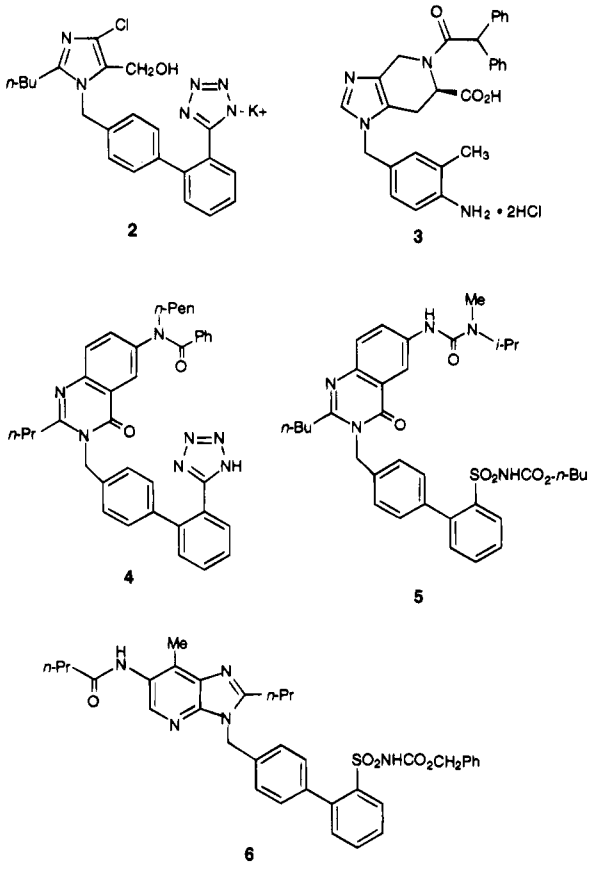
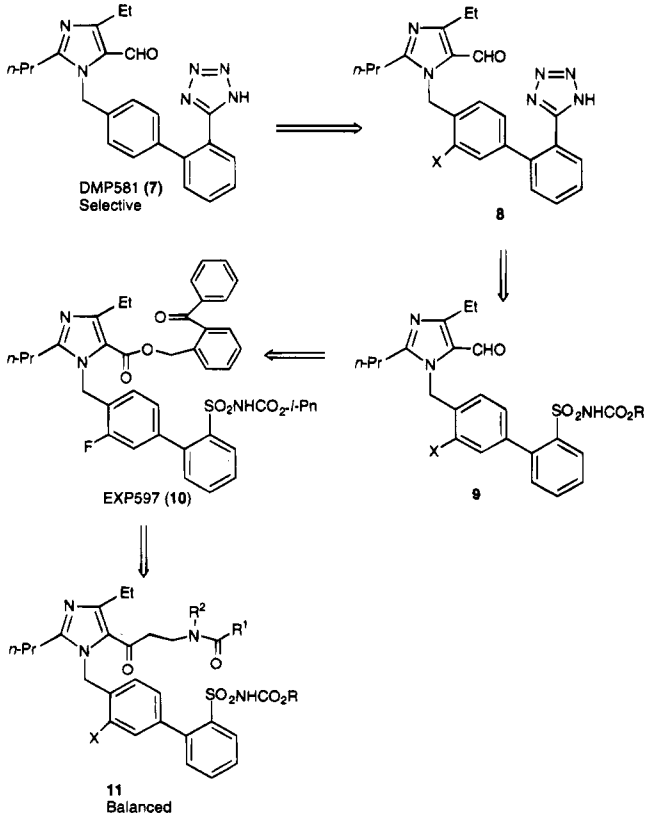


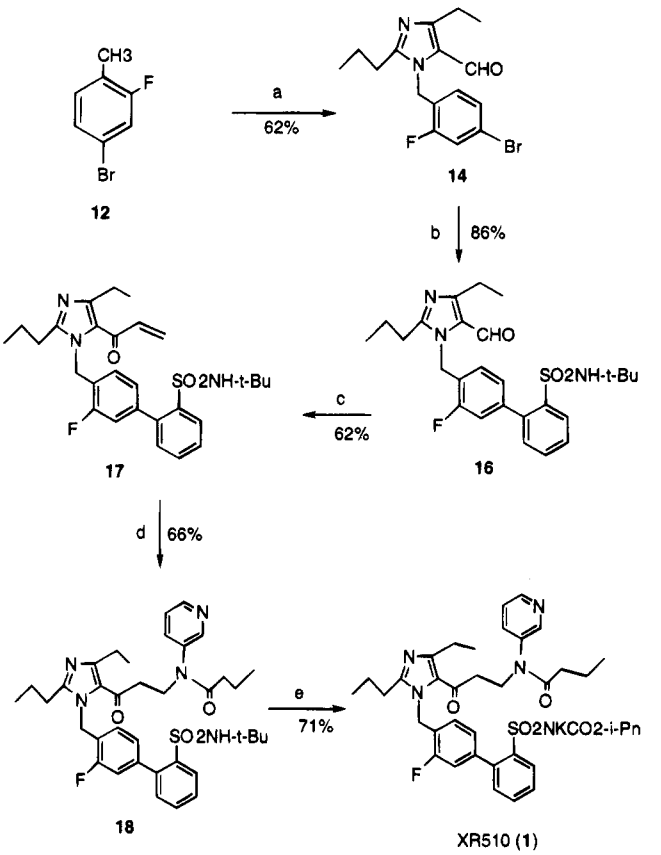
Figure 1. Structures of angiotensin II receptor antagonists.

Scheme 2. From AT_1 Selective to Balanced AT_1/AT_2 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]



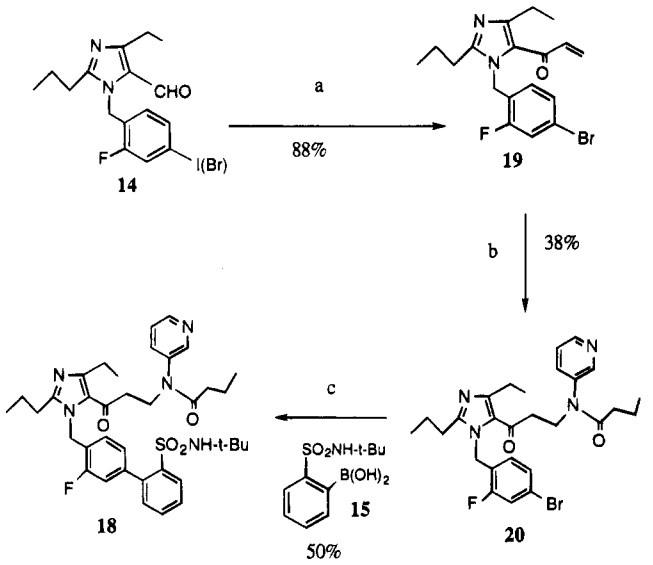
[a] (a) (1) NBS/AIBN, (2) 4-ethyl-5-formyl-2-propyl-1*H*-imidazole (13), K_2CO_3/DMF; (b) [2-[(*tert*-butylamino)sulfonyl]phenyl]boronic acid (15), $(PPh_3)_4Pd/Na_2CO_3$; (c) (1) CH_2=$CHMgBr$, (2) MnO_2; (d) (1) 3-aminopyridine/Et_3N, (2) butyryl chloride/Et_3N; (e) (1) TFA, (2) i-PnOCOCl/pyridine/DMAP, (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 **13**[15] yielded the (4-bromobenzyl)imidazole **14**. Compound **14** was then coupled with boronic acid **15**[19] 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 MnO_2 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 sulfonylcarbamate 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 MnO_2. 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) CH_2=CHMgBr, (2) MnO_2/CH_2Cl_2; (b) (1) 3-aminopyridine/Et_3N, (2) butyryl chloride/Et_3N; (c) $(PPh_3)_4Pd$/aqueous Na_2CO_3, toluene.

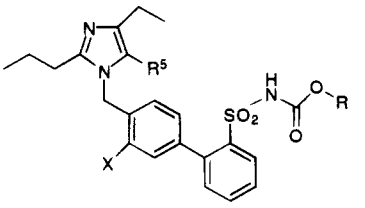
Results and Discussion

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 assay[5] 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 conditions[17] in which the radioligand [^{125}I][Sar^1,Ile^8]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 groups. For compounds where R^1 = R^2 = 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 1. Comparison of Binding Affinities in Original and Modified Assay Conditions[a]

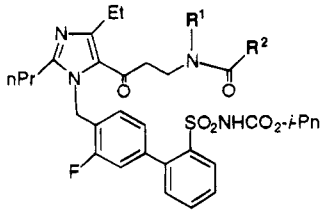


EXP929 (21): R^5 =CO_2Me; X = Cl; R = n-Bu
EXP408 (22): R^5 =CO_2Me; X = F; R = i-Pn
EXP970 (23): R^5 =COMe; X = F; R = n-Bu

compd	assay	IC_{50} (nM)[b] AT_1	IC_{50} (nM)[b] AT_2	AT_2/AT_1 ratio
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][Sar^1,Ile^8]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.

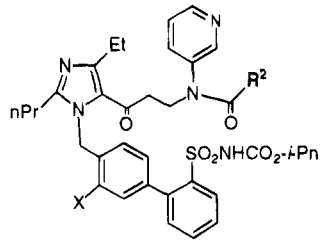
Table 2. Binding Affinities



compd	R^1	R^2	IC_{50} (nM)[a] AT_1	IC_{50} (nM)[a] AT_2	AT_2/AT_1 IC_{50} ratio	ED_{30} (mg/kg) po[b]
24	*n*-propyl	*n*-propyl	0.20	5.0	25	not tested
25	*n*-propyl	phenyl	0.20	4.0	20	<3.0
26	*n*-butyl	phenyl	0.30	10	33	not tested
27	phenyl	phenyl	0.25	0.18	0.70	1.57
28	phenyl	*n*-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	*n*-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]-[Sar^1,Ile^8]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.

Table 3. "Ortho" Substitution Effect



compd	X	R^2	IC_{50} (nM)[a] AT_1	IC_{50} (nM)[a] AT_2	AT_2/AT_1 IC_{50} ratio
34	F	*n*-propyl	0.32	0.25	0.78
38	H	*n*-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 [^{125}I]-[Sar^1,Ile^8]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.

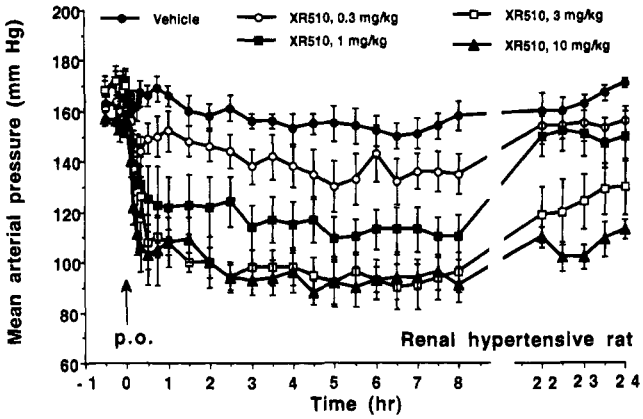


Figure 2. Effects of vehicle (0.05 mg/mL Na_2CO_3 in 0.5% methocel) and XR510 given po on mean arterial pressure in conscious renal hypertensive rats. Values represent the means ± SEM and $n = 6-9$ per group.

were obtained, but the 3-pyridyl derivative **32** had better oral potency as shown by its ED_{30} value. For compounds where R^1 is 3-pyridyl and R^2 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) R^2 substituents yielded compounds with 4−10-fold higher AT_2/AT_1 IC_{50} 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 AT_1 affinities were similar, the AT_2 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 [^{125}I][Sar^1,Ile^8]Ang II to the AT_1 and AT_2 receptors with IC_{50}s of 0.32 and 0.25 nM, respectively. In conscious renal hypertensive rats,[19] XR510 decreased blood pressure with an oral ED_{30} 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 ED_{30} 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 AT_1 and AT_2 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 ED_{30} 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 AT_1 or AT_2 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] [^{125}I][Sar^1,Ile^8]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 concious 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 ≤0.4% of the calculated values. Mass spectra were obtained on a HP 5988A MS/HP Partical Bean Interface. Chromatography was done using EM Science silica gel 60. Radiolabeled [^{125}I]Ang II was obtained from Du Pont NEN Products (Boston, MA).

1-(4-Bromo-2-fluorobenzyl)-4-ethyl-5-formyl-2-propyl-1*H*-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 CCl_4 (150 mL) was refluxed under N_2 for 4 h. The mixture was cooled, and the solid was filtered off and washed with CCl_4. The filtrate was washed with water and brine, dried over $MgSO_4$, 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-1*H*-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 N_2. The mixture was poured into water and extracted with EtOAc. The combined organic mixture was washed with H_2O and brine, dried over $MgSO_4$, 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%). ^{1}H NMR ($CDCl_3$): δ 0.95 (t, 3H, CH_3), 1.32 (t, 3H, CH_3), 1.70 (m, 2H, CH_2), 2.60 (m, 2H, CH_2), 2.85 (q, 2H, CH_2), 5.52 (s, 2H, $ArCH_2$), 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 N_2 for 20 h. The solvent was removed *in vacuo*, and the residue was partitioned between H_2O and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2, and the combined organic solution was washed with brine, dried over $MgSO_4$, 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). ^{1}H NMR ($CDCl_3$): δ 0.99 (t, 3H, CH_3), 1.01 (s, 9H, CH_3), 1.36 (t, 3H, CH_3), 1.73 (m, 2H, CH_2), 2.67 (m, 2H, CH_2), 2.90 (q, 2H, CH_2), 3.57 (s, 1H, NH), 5.62 (s, 2H, $ArCH_2$), 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 N_2 for 1.5 h. It was then quenched with 1 N aqueous HCl. After the THF was removed, the mixture was extracted with CH_2Cl_2. The organic solution was washed with H_2O and brine, dried over $MgSO_4$, and concentrated to an orange oil. The resulting oil was dissolved in 40 mL of CH_2Cl_2, and manganese(IV) oxide (8.0 g) was added. The resulting mixture was stirred at room temperature under N_2 for 24 h. The mixture was filtered through Celite and washed with CH_2Cl_2. 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). ^{1}H NMR ($CDCl_3$): δ 0.98 (t, 3H, CH_3), 0.99 (s, 9H, CH_3), 1.24 (t, 3H, CH_3), 1.77 (m, 2H, CH_2), 2.63 (m, 2H, CH_2), 2.90 (q, 2H, CH_2), 3.50 (s, 1H, NH), 5.59 (s, 2H, $ArCH_2$), 5.79 (d, 1H, CH), 6.31 (d, 1H, CH), 6.71 (t, 1H, ArH), 6.95 (m, 2H, CH_2=), 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 N_2 for 1 h. It was then quenched with 100 mL of 1 N aqueous HCl. The mixture was extracted with CH_2Cl_2, and the organic solution was washed with H_2O and brine, dried over $MgSO_4$, and concentrated to an orange oil. The resulting oil was dissolved in CH_2Cl_2 and manganese(IV) oxide (79.97 g, 920 mmol) was added. The resulting mixture was stirred at room temperature under N_2 overnight. The mixture was filtered through Celite and washed with CH_2Cl_2. 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%). ^{1}H NMR ($CDCl_3$): δ 0.95 (t, 3H, CH_3), 1.30 (t, 3H, CH_3), 1.70 (m, 2H, CH_2), 2.60 (m, 2H, CH_2), 2.88 (q, 2H, CH_2), 5.48 (s, 2H, $ArCH_2$), 5.80 (d, 1H, CH=), 6.30 and 6.62 (d, 2H, $=CH_2$), 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 N_2 for 48 h. The solvent was removed *in vacuo*. The residue was dissolved in EtOAc and washed with H_2O and brine. The organic solution was then dried over $MgSO_4$ and concentrated. The crude mixture was chromatographed on silica gel with 5% MeOH/CH_2Cl_2 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 N_2 for 3 h. The solvent was removed *in vacuo*. The residue was dissolved in EtOAc and washed with H_2O, 1 N NaOH, and brine. The organic solution was then dried over $MgSO_4$, concentrated, and chromatographed on silica gel with 5% MeOH/CH_2Cl_2 (1.83 g, 38% yield). MS: 543 [M + H]. ^{1}H NMR ($CDCl_3$): δ 0.79 (t, 3H, CH_3), 0.94 (t, 3H, CH_3), 1.31 (t, 3H, CH_3), 1.48–1.73 (m, 4H, CH_2), 1.94 (t, 2H, CH_2), 2.53 (t, 2H, CH_2), 2.90 (q, 2H, CH_2), 3.08 (t, 2H, CH_2), 3.97 (t, 2H, CH_2), 5.38 (s, 2H, $ArCH_2$), 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 N_2 for 12 h. TLC (4/6 hexane/ethyl acetate) still showed starting material. Half an equivalent of 3-aminopyridine (0.64 g) and Et_3N 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 H_2O and brine. The organic solution was then dried over $MgSO_4$ 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 $MgSO_4$ 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 N_2 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 H_2O, 1 N NaOH, and brine. The organic solution was then dried over $MgSO_4$ 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 N_2 for 4.5 h. The solvent was removed *in vacuo*, and the residue was partitioned between H_2O and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2, and the combined organic solution was washed with brine, dried over $MgSO_4$, and concentrated. The crude product was purified by flash column chromatography (silica gel, 5% MeOH/CH_2Cl_2) to give 1.15 g of pale yellow foam (50%). MS: 677 (M + H). ^{1}H NMR ($CDCl_3$): δ 0.81 (t, 3H, CH_3), 0.96 (t, 3H, CH_3), 0.99 (s, 9H, CH_3), 1.32 (t, 3H, CH_3), 1.57 (m, 2H, CH_2), 1.68 (m, 2H, CH_2), 1.95 (t, 2H, CH_2), 2.58 (t, 2H, CH_2), 2.88 (q, 2H, CH_2), 3.08 (t, 2H, CH_2), 3.96 (s, 1H, NH), 3.98 (t, 2H, CH_2), 5.48 (s, 2H, $ArCH_2$), 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 N_2 for 12 h. The solvent was removed *in vacuo*. The residue was dissolved in CH_2Cl_2 and washed with aqueous $NaHCO_3$ 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 CH_2Cl_2 (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 N_2 for 56 h. The reaction mixture was diluted with CH_2Cl_2 and washed with 10% of aqueous citric acid and brine. It was dried over $MgSO_4$ and concentrated. The crude product mixture was purified by flash column chromatography (silica gel, 5% MeOH in CH_2Cl_2) to give 4.6 g of compound **34** (71% yield). MS: 735 [M + H]. ^{1}H NMR ($CDCl_3$): δ 0.77 (t, 3H, CH_3), 0.85 (d, 6H, CH_3), 0.94 (t, 3H, CH_3), 1.34 (t, 3H, CH_3), 1.38–1.60 (m, 5H, CH and CH_2), 1.70 (m, 2H, CH_2), 1.95 (t, 2H, CH_2), 2.52 (t, 2H, CH_2), 2.93 (q, 2H, CH_2), 3.21 (br s, 2H, CH_2), 4.08 (t, 4H, CH_2), 5.50 (br s, 2H, CH_2Ar), 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. ($C_{39}H_{48}FN_5O_6S$) C, H, N.

Compound **34** (0.67 g) was dissolved in 50 mL of MeOH and 5 mL of H_2O. 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 $CHCl_3/CH_3OH$ and then precipitated with hexane to give 0.58 g of off-white solid (**1**, XR510). ^{1}H NMR ($CDCl_3$): δ 0.69 (t, 3H, CH_3), 0.70 (d, 6H, CH_3), 0.90 (t, 3H, CH_3), 1.19 (m, 5H, CH_2 and CH_3), 1.44 (m, 3H, CH and CH_2), 1.64 (m, 2H, CH_2), 1.85 (t, 2H, CH_2), 2.54 (t, 2H, CH_2), 2.74 (q, 2H, CH_2), 2.90 (t, 2H, CH_2), 3.70 (t, 2H, CH_2), 4.03 (t, 2H, CH_2), 5.24 (s, 2H, CH_2Ar), 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. ($C_{39}H_{47}FN_5O_6SK$) 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]. ^{1}H NMR (DMSO-d_6): δ 0.72–0.98 (m, 12H, CH_3), 1.312–1.57 (m, 10H, CH, CH_2, CH_3), 1.59–1.66 (m, 2H, CH_2), 2.17–2.30 (m, 2H, CH_2), 2.58 (m, 2H, CH_2), 2.80–3.22 (m, 6H, CH_2), 3.40–3.61 (m, 6H, CH_2), 5.58 (s, 2H, CH_2Ar), 6.42 (m, 1H, ArH), 7.09 (m, 2H, ArH), 7.38 (m, 2H, ArH), 7.96 (m, 1H, ArH). Anal. ($C_{36}H_{49}FN_4O_6S\cdot1.5H_2O$) 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]. ^{1}H NMR ($CDCl_3$): δ 0.72–1.82 (m, 20H, CH_2, CH_3), 2.53–3.42 (m, 8H, CH_2), 3.70 (m, 2H, CH_2), 3.95 (t, 2H, CH_2), 5.58 (s, 2H, CH_2Ar), 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. ($C_{39}H_{47}FN_4O_6S$) 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]. ^{1}H NMR ($CDCl_3$): δ 0.72–1.02 (m, 9H, CH_3), 1.12–1.61 (m, 11H, CH_2, CH_3), 1.74 (m, 2H, CH_2), 2.75 (t, 2H, CH_2), 2.86–3.76 (m, 6H, CH_2), 3.72 (t, 2H, CH_2), 3.96 (t, 2H, CH_2), 5.58 (s, 2H, CH_2Ar), 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]. ^{1}H NMR ($CDCl_3$): δ 0.85 (t, 3H, CH_3), 0.98 (t, 3H, CH_3), 1.20 (m, 2H, CH_3), 1.27 (t, 2H, CH_2), 1.42 (m, 2H, CH_2), 1.75 (m, 2H, CH_2), 2.65 (t, 2H, CH_2), 2.85 (q, 2H, CH_2), 3.15 (t, 2H, CH_2), 3.95(t, 2H, CH_2), 4.20 (t, 2H, CH_2), 5.50 (s, 2H, CH_2Ar), 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 ($C_{42}H_{44}FN_4O_6SK\cdot2H_2O$) 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]. ^{1}H NMR ($CDCl_3$): δ 0.80 (t, 3H, CH_3), 0.85 (t, 3H, CH_3), 0.99 (t, 3H, CH_3), 1.20 (m, 2H, CH_3), 1.26 (t, 2H, CH_2), 1.47 (m, 2H, CH_2), 1.58 (m, 2H, CH_2), 1.75 (m, 2H, CH_2), 2.01 (t, 2H, CH_2), 2.66 (t, 2H, CH_2), 2.84 (q, 2H, CH_2), 3.01 (t, 2H, CH_2), 3.91(t, 2H, CH_2), 4.00 (t, 2H, CH_2), 5.50 (s, 2H, CH_2Ar), 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 ($C_{39}H_{46}FN_4O_6SK$) 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]. ^{1}H NMR ($CDCl_3$): δ 0.77 (d, 6H, CH_3), 0.97 (t, 3H, CH_3), 1.20 (t, 3H, CH_3), 1.31 (m, 2H, CH_2), 1.48 (m, 1H, CH), 1.70 (m, 2H, CH_2), 2.59 (t, 2H, CH_2), 2.77 (q, 2H, CH_2), 3.06 (t, 2H, CH_2), 3.79 (t, 2H, CH_2), 4.29 (t, 2H, CH_2), 5.24 (s, 2H, CH_2Ar), 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. ($C_{43}H_{47}FN_4O_6S$) 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]. ^{1}H NMR ($CDCl_3$): δ 0.81 (d, 6H, CH_3), 0.96 (t, 3H, CH_3), 1.20–1.48 (m, 6H, CH, CH_2, CH_3), 1.70 (m, 2H, CH_2), 2.61 (t, 2H, CH_2), 2.83 (q, 2H, CH_2), 3.09 (t, 2H, CH_2), 3.98 (t, 2H, CH_2), 4.19 (t, 2H, CH_2), 5.47 (s, 2H, CH_2Ar), 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. ($C_{42}H_{46}FN_5O_6S$) 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]. ^{1}H NMR ($CDCl_3$): δ 0.83 (d, 6H, CH_3), 0.95 (t, 3H, CH_3), 1.19–1.32 (m, 4H, CH, CH_3), 1.70 (m, 2H, CH_2), 2.52 (t, 2H, CH_2), 2.95 (q, 2H, CH_2), 3.32 (br s, 2H, CH_2), 4.01 (t, 2H, CH_2), 4.34 (br s, 2H, CH_2), 5.40 (br s, 2H, CH_2Ar), 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 ($C_{41}H_{44}FN_6O_6SK\cdot{}^1/_2H_2O$) 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]. ^{1}H NMR ($CDCl_3$): δ 0.86 (d, 6H, CH_3), 0.97 (t, 3H, CH_3), 1.38 (t, 3H, CH_3), 1.38 (m, 2H, CH_2), 1.50 (m, 1H, CH), 1.72 (m, 2H, CH_2), 2.52 (t, 2H, CH_2), 2.98 (q, 2H, CH_2), 3.34 (br s, 2H, CH_2), 4.00 (t, 2H, CH_2), 4.38 (br s, 2H, CH_2), 5.40 (br s, 2H, CH_2Ar), 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. ($C_{41}H_{45}FN_6O_6S$) 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]. ^{1}H NMR ($CDCl_3$): δ 0.75 (d, 6H, CH_3), 0.87 (t, 3H, CH_3), 0.93 (t, 3H, CH_3), 1.26 (m, 2H, CH_2), 1.47 (m, 1H, CH), 1.68 (m, 2H, CH_2), 2.58 (t, 2H, CH_2), 2.84 (q, 2H, CH_2), 3.24 (t, 2H, CH_2), 3.77 (t, 2H, CH_2), 4.38 (t, 2H, CH_2), 5.28 (br s, 2H, CH_2Ar), 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 ($C_{41}H_{45}FN_6O_6SK\cdot2H_2O$) 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]. ^{1}H NMR ($CDCl_3$): δ 0.84 (d, 6H, CH_3), 0.93 (m 9H, CH_3), 1.33 (t, 3H, CH_3), 1.42 (t, 2H, CH), 1.47 (m, 1H, CH), 1.68 (m, 2H, CH_2), 2.34 (m, 2H, CH), 2.52 (t, 2H, CH_2), 2.95 (q, 2H, CH_2), 3.20 (br.s,, 2H, CH_2), 4.07 (t, 4H, CH_2), 5.28 (br s, 2H, CH_2Ar), 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 ($C_{39}H_{48}FN_5O_6SK\cdot H_2O$) 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]. ^{1}H NMR ($CDCl_3$): δ 0.83 (d, 6H, CH_3), 0.95 (t, 3H, CH_3), 1.33 (t, 3H, CH_3), 1.42 (m, 3H, CH and CH_2), 1.70 (m, 2H, CH_2), 1.97 (t, 2H, CH_2), 2.52 (t, 2H, CH_2), 2.91 (q, 2H,

CH_2), 3.10 (br s, 2H, CH_2), 4.08 (t, 4H, CH_2), 5.41 (br s, 2H, CH_2Ar), 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. ($C_{38}H_{46}FN_5O_6S$) C, H, N.

1-[[2′-[[(Isopentoxycarbonyl)amino]sulfonyl]-3-fluoro-(1,1′-biphenyl)-4-yl]methyl]-5-[3-(*N*-pyridin-3-ylethanamido)propanoyl]-4-ethyl-2-propyl-1*H*-imidazole (37). MS: 706 [M + H]. ^1H NMR ($CDCl_3$): δ 0.90 (d, 6H, CH_3), 0.92 (t, 3H, CH_3), 1.22 (t, 3H, CH_3), 1.38 (m, 2H, CH_2), 1.55 (m, 3H, CH, CH_2), 2.30 (t, 2H, CH_2), 2.46 (br s, 3H, CH_3), 2.80 (q, 2H, CH_2), 3.18 (m, 2H, CH_2), 4.02 (t, 2H, CH_2), 4.18 (t, 2H, CH_2), 5.18 (s, 2H, CH_2Ar), 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-1*H*-imidazole (38). MS: 716 [M + H]. ^1H NMR ($CDCl_3$): δ 0.76 (t, 3H, CH_3), 0.85 (d, 6H, CH_3), 0.93 (t, 3H, CH_3), 1.35 (t, 3H, CH_3), 1.42 (m, 2H, CH_2), 1.46 (m, 1H, CH), 1.50 (m, 2H, CH_2), 1.70 (m, 2H, CH_2), 1.92 (t, 2H, CH_2), 2.65 (t, 2H, CH_2), 2.97 (q, 2H, CH_2), 3.24 (m, 2H, CH_2), 4.07 (m, 4H, CH_2), 5.48 (br s, 2H, CH_2Ar), 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 ($C_{39}H_{48}FN_5O_6SK\cdot KOH$) 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-1*H*-imidazole (39). MS: 751 [M + H]. ^1H NMR ($CDCl_3$): δ 0.83 (d, 6H, CH_3), 0.87 (t, 3H, CH_3), 1.25 (t, 3H, CH_3), 1.35 (m, 3H, CH_2, CH), 1.70 (m, 2H, CH_2), 2.52 (t, 2H, CH_2), 2.95 (q, 2H, CH_2), 3.32 (t, 2H, CH_2), 3.99 (t, 2H, CH_2), 4.34 (t, 2H, CH_2), 5.39 (s, 2H, CH_2Ar), 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 ($C_{41}H_{45}FN_6O_6SK\cdot H_2O$) C, H, N.

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