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Balanced Angiotensin II Receptor Antagonists. III. The Effects of Substitution at the Imidazole 5-Position.[1a, b]

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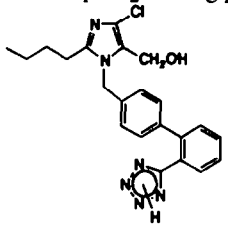
Abstract: We wish to report on a series of substituted methyl esters and amides of DMP 811, which bind to both the AT_1 and AT_2 receptor subtypes. Some of the esters bind well to both receptor subtypes in the subnanomolar range when the optimal acid isostere is present together with an ortho-fluorine substituent on the biphenylmethyl group.

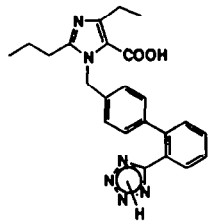
The angiotensin II (AII) antagonist losartan is currently in Phase III clinical trials for the treatment of hypertension.[2] It acts by specific blockade of the angiotensin II subtype 1(AT_1) receptor which is responsible for the immediate pressor response induced by angiotensin II. A second subtype of angiotensin II receptor (AT_2) has also been identified in a variety of tissues[3] using AT_2 selective ligands discovered at Parke-Davis, such as PD123,177.[4] The physiological action governed by the AT_2 receptor has not been clearly defined as of yet.[1b, 5]

AT_1-selective antagonists increase plasma renin activity and therefore circulating levels of AII.[6] Angiotensin II binds to both the AT_1 and AT_2 sites with a slightly greater affinity for the AT_2 receptor.[7] Since it is not clear what effects (either positive or negative) chronic AT_2 stimulation would produce when AT_1-selective drugs are dosed chronically, it seemed reasonable to develop compounds which would bind to both angiotensin II receptor subtypes.[8]

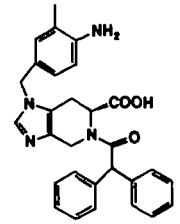
An important pharmacophore in the Parke-Davis series is the large lipophilic amide substituent on the piperidine ring.[4] Thus to introduce AT_2 binding activity into losartan, we believed that we had to incorporate an additional judiciously placed large lipophilic group into the molecule. It was not obvious at what position this should be done. DMP 811 is a second generation AII antagonist, similar in many respects to losartan, and it is a potent antihypertensive in its own right (ED_{30} =0.005 mg/kg i.v.; ED_{30}=0.03 mg/kg p.o., renal hypertensive rat (RHR)).[9] We therefore decided to see what effect the synthesis of large lipophilic esters of DMP 811 would have on the AT_1/AT_2 binding profile.



Losartan (DuP 753, Cozaar®)



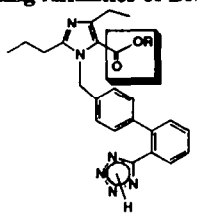
DMP 811



PD123,177

Indeed esterification of DMP811 with bulky lipophilic amide groups yielded compounds which showed AT_2 receptor affinity while retaining AT_1 affinity. Molecular modeling suggested that incorporation of the benzoylbenzyl side-chain (ex. **11-13**) could replace the diphenyl amide group. Of these, only the ortho-isomer (ex. **11**) retained good AT_2 affinity. Removal of the carbonyl group (ex. **14**) lowered the AT_2 affinity by one order of magnitude leading us to believe that this carbonyl group might be participating in an H-bond with the receptor (see also exs. **22** versus **43**, Table 3).

Table 1. Binding Affinities of DMP 811 Esters.



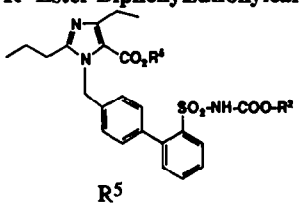
Ex. No.	R	IC_{50} (nM)[11]	
		AT_1	AT_2
DMP 811	H	6 (4)	>1000
4	$(Ph)_2N$-CO-C≡C-CH_2-	40	600
5	(n-Bu)(Bn)N-CO-C≡C-CH_2-	10	400
6	(n-Bu)(Bn)N-CO-CH_2-CH_2-CH_2-	10	300
7	$(n\text{-}Bu)_2N$-CO-CH_2-CH_2-CH_2-	30	500
8	4-[$(Ph)_2N$-CO-]$PhCH_2$-	20	200
9	3-[$(Ph)_2N$-CO-]$PhCH_2$-	30	300
10	4-[(Bn)(n-Bu)N-CO-]$PhCH_2$-	8 (0.7)	200 (70)
11	2-(Ph-CO-)$PhCH_2$-	2	300
12	3-(Ph-CO-)$PhCH_2$-	9	1000
13	4-(Ph-CO-)$PhCH_2$-	9	2000
14	2-(Ph)$PhCH_2$-	3	2000
15	4-(Ph)$PhCH_2$-	3	3000

The values in parentheses for DMP811 and ex. **10** in Table 1 are the binding affinities obtained by a modified assay.[10] This assay generally displays a greater divergence between the AT_1 and AT_2 binding affinities compared to the original assay.[11] Because we sought compounds which would show maximum AT_2 blockade at antihypertensive dosage levels, it was decided that the more stringent modified assay should be used in all subsequent work. Thus compounds in Tables 2-4 were tested using the modified assay.

We learned from our collaboration with Merck Research Laboratories[12] that an enhancement in the AT_2 binding affinity is observed when a lipophilic sulfonylcarbamate acid isostere is used instead of a tetrazole. Table 2 summarizes the benzoylbenzyl side-chain-containing sulfonylcarbamates. Immediately we notice that the AT_2 affinity tends to be improved. The isoamylcarbamate is the best acid isostere (ex. **18**).

We have previously found that substitution of an ortho-fluoro group on the biphenyl group increases the AT_2 affinity.[1a, 13] Addition of an ortho-fluoro group onto the biphenylsulfonylcarbamate moiety yielded the compounds in Table 3. This modification led to compounds with nearly equal ("balanced") affinities for both the AT_1 and AT_2 receptors. Substituting various other H-bonding groups in place of the carbonyl group led to compounds that were less balanced. The benzoylbenzyl side-chain produced the most balanced compounds. For example, replacement of the C=O group of ex. 22 with -O-, -S-, -SO-, -SO_2-, -NH-CO-, and -CO-NH- (exs. **27**, **43-45** **55**, and **56**) led to good AT_1 binding, but slightly less potent AT_2 binding. The decreased AT_2 affinity of ex. **43** relative to that of ex. **22** suggests the importance of the C=O group in binding to the

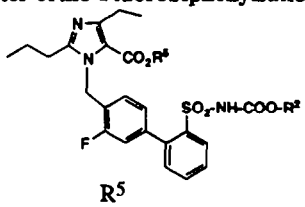
Table 2. R^5 Ester Biphenylsulfonylcarbamates.



Ex. No.	R^2	R^5	IC_{50} (nM)[10] AT_1	AT_2
16	methyl	2-(Ph-CO-)$PhCH_2$-	0.6	10
17	phenethyl	2-(Ph-CO-)$PhCH_2$-	0.74	2.1
18	isoamyl	2-(Ph-CO-)$PhCH_2$-	0.35	1.9

AT_2 receptor. The 2-thiophenyl analog (ex. **28**) shows more potent AT_2 binding affinity than its 3-thiophenyl isomer (ex. **30**). An explanation for this is that the sulfur atom of **28** can better mimic the position of the carbonyl oxygen atom of the 2-(Ph-CO-)$PhCH_2$- side-chain of ex. **22**. Interestingly, the (pyrid-2-yl)benzyl analog (ex. **33**) shares the same binding affinity as the 2-thiophen-2-yl analog **28**. Here the pyridyl nitrogen also mimics the position of the carbonyl oxygen atom of the 2-(Ph-CO-)$PhCH_2$- side-chain of ex. **22**. Replacement of the ester by an amide (Table 4) led to only a slight loss in AT_2 binding affinity.

Table 3. R^5 Ester ortho-Fluorobiphenylsulfonylcarbamates.

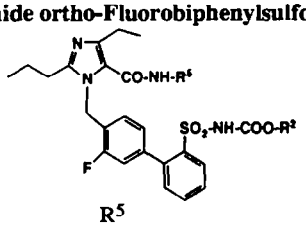


Ex. No.	R^2	R^5	IC_{50} (nM)[10] AT_1	AT_2
19	phenethyl	2-(Ph-CO-)$PhCH_2$-	0.57	0.69
20	n-propyl	2-(Ph-CO-)$PhCH_2$-	0.28	1.6
21	isobutyl	2-(Ph-CO-)$PhCH_2$-	0.5	1.0
22	isoamyl	2-(Ph-CO-)$PhCH_2$-	0.5	0.7
23	n-butyl	2-(Ph-CO-)$PhCH_2$-	0.2	0.9
24	isoamyl	3-(Ph-CO-)$PhCH_2$-	0.6	0.9
25	n-propyl	3-(Ph-CO-)$PhCH_2$-	0.3	10
26	isoamyl	2-(t-butyl-CO-)$PhCH_2$-	0.3	3
27	n-butyl	2-(Ph-O-)$PhCH_2$-	0.6	3
28	isoamyl	2-(thiophen-2-yl)$PhCH_2$-	0.8	3
29	n-propyl	2-(thiophen-2-yl)$PhCH_2$-	0.5	3
30	isoamyl	2-(thiophen-3-yl)$PhCH_2$-	0.6	20
31	n-propyl	2-(thiophen-3-yl)$PhCH_2$-	0.3	20
32	n-propyl	2-(pyrimidin-5-yl)$PhCH_2$-	0.8	10
33	isoamyl	2-(pyrid-2-yl)$PhCH_2$-	0.3	3
34	isoamyl	2-(Ph)$PhCH_2$-	3	9
35	isoamyl	$PhOCH_2CH_2CH_2CH_2$-	0.2	2
36	isoamyl	$PhOCH_2CH_2CH_2$-	0.1	2
37	isoamyl	$PhCH_2OCH_2CH_2CH_2$-	0.1	2
38	isoamyl	(N-phthalimido)CH_2CH_2-	0.2	7
39	isoamyl	(N-phthalimido)$CH_2CH_2CH_2$-	0.1	3
40	isoamyl	2-(CH_3O-)$PhCH_2$-	0.1	1
41	heptyl	2-(CH_3O-)$PhCH_2$-	1	10
42	isoamyl	2-(isoamyloxy)$PhCH_2$-	3	10

Table 3., continued.

Ex. No.	R^2	R^5	IC_{50} (nM)[10] AT_1	AT_2
43	isoamyl	2-(Ph-S-)$PhCH_2$-	1	2
44	isoamyl	2-(Ph-SO-)$PhCH_2$-	0.2	2
45	isoamyl	2-(Ph-SO_2-)$PhCH_2$-	0.4	5
46	isoamyl	Ph-CO-$CH_2CH_2CH_2$-	0.1	5
47	isoamyl	Ph-CO-CH_2-	0.1	2
48	isoamyl	PhS-$CH_2CH_2CH_2$-	0.2	2
49	isoamyl	Ph-SO-$CH_2CH_2CH_2$-	0.2	1
50	isoamyl	Ph-SO_2-$CH_2CH_2CH_2$-	0.2	2
51	isoamyl	(n-Bu)(Bn)N-CO-$(CH_2)_3$-	0.2	5
52	isoamyl	(Ph)(H)N-CO-$(CH_2)_3$-	0.2	5
53	isoamyl	(Ph)(H)N-CO-$(CH_2)_2$-	0.1	3
54	n-pentyl	(Ph)(H)N-CO-$(CH_2)_2$-	0.1	1
55	isoamyl	2-(Ph-CO-NH-)$PhCH_2$-	0.3	1
56	isoamyl	2-(Ph-NH-CO-)$PhCH_2$-	0.3	1
57	isoamyl	Ph-CO-CH(Ph)-	0.8	3
58	isoamyl	isoamyloxy-CO-N(Ph)-$(CH_2)_2$-	0.2	4
59	isoamyl	Ph-CO-N(Ph)-$(CH_2)_2$-	0.1	2

Table 4. R^5 Amide ortho-Fluorobiphenylsulfonylcarbamates.

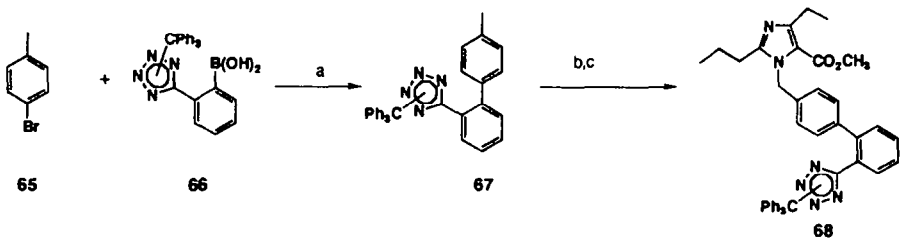


Ex. No.	R^2	R^5	IC_{50} (nM)[10] AT_1	AT_2
61	isoamyl	$PhOCH_2CH_2CH_2$-	0.3	9
62	n-butyl	$PhOCH_2CH_2CH_2$-	0.4	20
63	isoamyl	2-(Ph-S-)$PhCH_2$-	0.4	3
64	isoamyl	2-(Ph-SO-)$PhCH_2$-	0.6	5

Synthesis

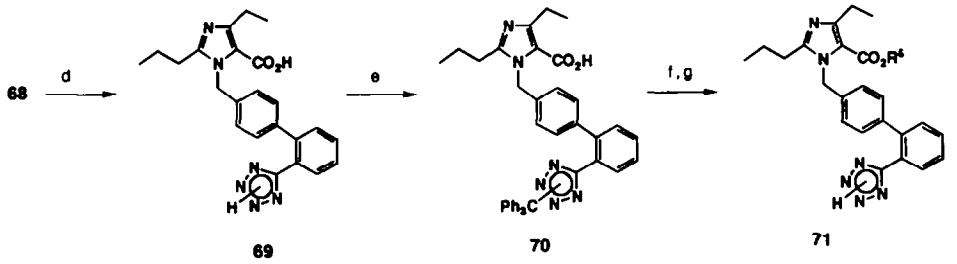
The esters in Table 1 were synthesized as shown in Scheme 1. Suzuki coupling[14] of bromide **65** with boronic acid **66**[15] yielded **67**. Benzylic bromination and alkylation yielded **68** which was simultaneously saponified and detritylated to yield carboxylic acid-tetrazole **69**. Tritylation (**70**), followed by esterification and detritylation yielded ester **71**. The esters in Tables 2 and 3 were made by the procedure outlined in Scheme 2. The carboxylic acid of biphenylsulfonamide **72**[16] was esterified to yield ester biphenylsulfonamide **74**. Reaction with a chloroformate yielded product **76**. The amides in Table 4 were made by converting **73** to an amide and hydrolysing the t-butyl group (**75**) followed by reaction with a chloroformate to yield product **77**.

Scheme 1



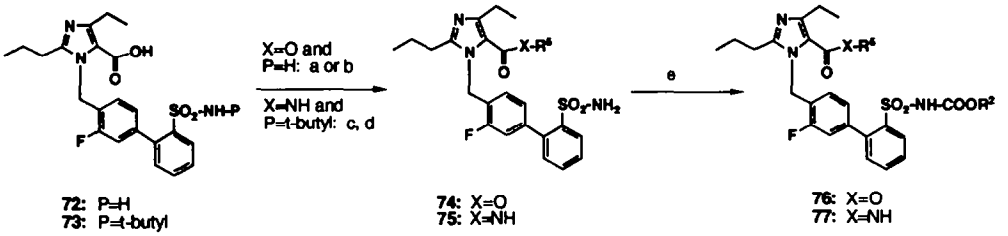
65 66 67 68

Scheme 1, continued.



Reagents: a. $(Ph_3P)_4Pd$, tetrabutylammonium bromide, sodium carbonate (aq), toluene, Δ, 4h; b. NBS, benzoyl peroxide, CCl_4, Δ; c. methyl 4-ethyl-2-n-propylimidazole-5-carboxylate, K_2CO_3, DMF, rt, 24h; d. 1.0 N NaOH, THF, MeOH, 60 °C, 48h; e. Ph_3CCl, Et_3N, CH_2Cl_2, rt, 4h; f. R^5Br or R^5OMs, K_2CO_3, DMF, rt, 24h; g. MeOH, reflux, 3h, followed by immediate silica gel chromatography

Scheme 2



Reagents: a. R^5-Br, K_2CO_3, DMF, rt, 24h; b. carbonyldiimidazole, THF, Δ, followed by R^5ONa; c. R^5NH_2, DCC, CH_3CN, rt; d. trifluoroacetic acid, rt; e. R^2OCOCl, DMAP, py, CH_2Cl_2, rt, 24h

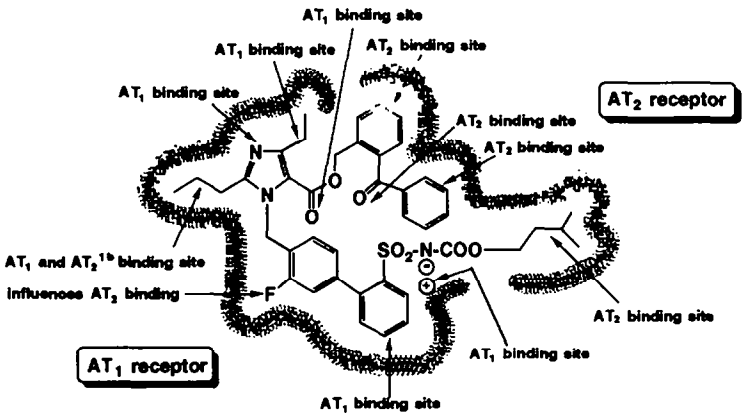


Figure 1. Pharmacophores required for binding to the AT_1 and AT_2 receptors.

Conclusion

We have successfully incorporated AT_2 binding affinity into DuP 753-like AT_1 antagonists, resulting in compounds displaying nearly equal binding affinities for both the AT_1 and AT_2 receptor subtypes. The critical features necessary for this dual binding affinity are summarized in Figure 1. In addition to binding, these

compounds also exhibit good i.v. and oral antihypertensive activity (ex. **20**, ED_{30} (RHR) = 0.08 mg/kg i.v. and 0.7 mg/kg p.o. and ex. **22**, ED_{30} (RHR) = 0.05 mg/kg i.v. and 0.9 mg/kg p.o.).

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