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BALANCED ANGIOTENSIN II RECEPTOR ANTAGONISTS. I. THE EFFECTS OF BIPHENYL "ORTHO"-SUBSTITUTION ON AT_1/AT_2 AFFINITIES

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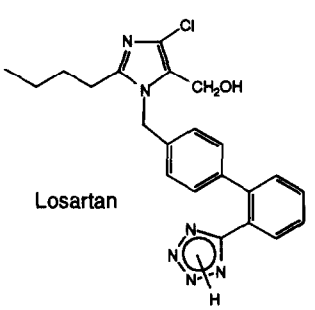
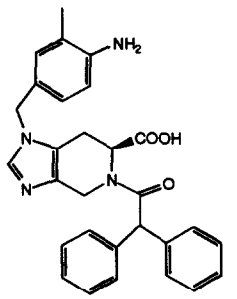
Abstract: Biphenyl "ortho"-substitution of DuP 753-like AT_1-selective angiotensin II receptor antagonists provides AT_2 affinity. When combined with a sulfonylcarbamate as the acid isostere, balanced AT_1/AT_2 receptor antagonists were obtained. Some compounds exhibited nanomolar affinities for both receptors and good AT_2/AT_1 ratios; these compounds also produce potent and prolonged antihypertensive effects in renal hypertensive rats.

The renin-angiotensin system (RAS) is known to play an important role in regulating and maintaining blood pressure.[1] Angiotensin II (Ang II) is the active hormone of the RAS, and it mediates a variety of physiologic functions through its receptors. There are at least two distinct Ang II receptor subtypes[2,3] designated as AT_1 and AT_2. The AT_1 receptor mediates most of the known Ang II physiologic functions, such as vasoconstriction. The potential role for nonpeptide Ang II receptor antagonists in the treatment of hypertension has been demonstrated by AT_1-selective Ang II antagonists such as Cozaar® (losartan, DuP 753).[4,5a] Recently some compounds with affinities for both receptors have been described,[6,7] however most of the Ang II antagonists reported are selective either for AT_1 (e.g. losartan) or for AT_2 (e.g. PD123,177).[5] The function of the AT_2 receptor is uncertain at this time, however, AT_2 mediated effects of Ang II have been implicated in renal free water clearance,[8] restenosis following vascular injury,[9] collagen synthesis in cardiac fibroblasts,[10] and depressor response to angiotensin II and III in rats.[11] While the clinical effects of AT_2 blockade are unknown, simultaneous inhibition of both receptors might prove advantageous.

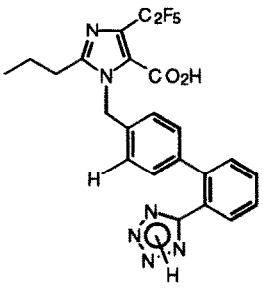


Losartan

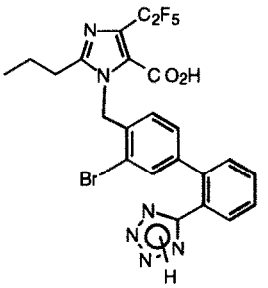


PD123,177

When the "ortho"-position of the biphenyl unit of DuP 532[12] was brominated[13] to give EXP332, the AT_2 affinity was increased by at least 100-fold. This interesting finding suggested a means of preparing balanced



DuP 532
IC_{50}:
AT_1 = 3 nM
AT_2 = >10,000 nM

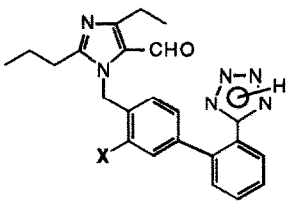


EXP332
IC_{50}:
AT_1 = 3 nM
AT_2 = 80 nM

Ang II receptor antagonists through modifications of AT_1-selective compounds. In order to minimize antihypertensive dosage levels while maximizing AT_2 blockade, we sought nonpeptide antagonists with AT_1 IC_{50} values of less than 10 nM and an AT_2/AT_1 IC_{50} ratio of less than five.

To explore this ortho effect, we prepared a series of ortho-substituted analogs of the 4-ethylimidazole DMP 581,[14] a compound of superior oral antihypertensive potency compared to DuP 532. The AT_2 affinity was increased by greater than 20-fold with appropriate substitution as demonstrated in Table 1. Although the AT_1 affinity decreased, it still remained in the range of 7-40 nM. Among these compounds, the chloride **2** gave the best combined results. The increase in AT_2 activity observed in this series was not sufficient to produce balanced compounds, but the ratio of AT_2/AT_1 was improved from over 5000 (DMP 581) to 50 (**2**).

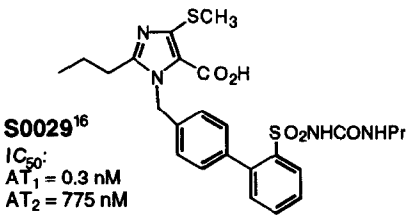
Table 1. "Ortho"-Substitution Effects in Biphenyl Tetrazoles



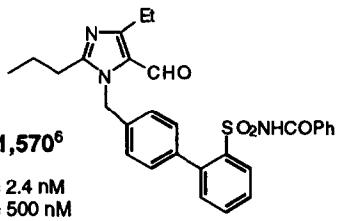
Compd.	X	[a]IC_{50} (AT_1, nM)	[a]IC_{50} (AT_2, nM)	[b]ED_{30} (mg/kg), *i.v.*
[14]DMP 581	H	2	>10,000	0.04
1	F	7	3,000	0.17
2	Cl	10	500	0.87
3	Br	20	700	1.05
4	CH_3	40	1,000	1.40

a. IC_{50} is the inhibitory concentration of potential Ang II antagonists which gives 50% displacement of the total specifically bound[^{125}I] Ang II to rat adrenal cortical microsomes. The intraassay and interassay variabilities of the IC values for a given compound are 5-10% and 15-30%, respectively. see reference 3 for more details.
b. ED_{30} is the effective dose to lower blood pressure by 30 mmHg in renal hypertensive rats (RHR). see reference 15 for details.

From our collaboration with the Merck Research Laboratories in the Ang II area, we became aware of the finding by Merck scientists that AT_2 affinity is frequently increased when the tetrazole is replaced by certain acyl sulfonamides and sulfonylcarbamates.[7c] In fact, the benzoyl sulfonamide analog (**L-161,570**) of DMP 581



S0029[16]
IC_{50}:
AT_1 = 0.3 nM
AT_2 = 775 nM



L-161,570[6]
IC_{50}:
AT_1 = 2.4 nM
AT_2 = 500 nM

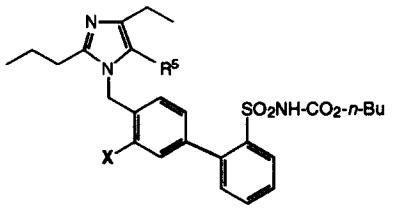
shows at least a 20-fold increase in AT_2 activity.[6] Hoechst has recently reported an imidazole (**S0029**) with good AT_1 and modest AT_2 affinity.[16] To further increase AT_2 affinity in our series, compounds containing both an ortho-substituent and a sulfonylcarbamate were synthesized and are described in Table 2. Compared with DMP 581, compound **5** showed at least a 1,000-fold increase in AT_2 activity. Ortho-substitution further improved the AT_2 affinity by 2 to 27 fold. Furthermore, the AT_1 activity was maintained in most cases. Fluoro-substitution improved the AT_1 affinity as well as the AT_2 affinity. The AT_2 activity was also affected by the R^5 group for those compounds where X=H. The AT_2 affinity of the R^5 aldehyde **5** was 4-fold greater than the R^5 methyl ester **8**, and 8-fold greater than the R^5 methyl ketone **14** . However, when an ortho-subtituent was present, the R^5 effect was smaller as demonstrated by the R^5 aldehyde **6** and the R^5 methyl ester **11**.

The structure-activity relationship (SAR) of various alkyl carbamates in combination with chloro and fluoro-substitutions was also investigated. *n*-Butyl and isoamyl were found to give the most potent activities for both receptors, and the isoamyl group produced a better AT_2/AT_1 ratio. The isoamyl derivative of **13** (**18**) showed an AT_2/AT_1 ratio of 1 (see Table 3). Similar to the results observed by the Merck Research Laboratories,[7c] smaller alkyl groups such as *n*-propyl and isobutyl , and larger groups such as *n*-hexyl, *i*-hexyl, and benzyl, provided less AT_2 activity. Some of the pharmacological data from our three best compounds is summarized in Table 3. These compounds exhibited nanomolar affinities for both the AT_1 and AT_2 receptors, and possessed good AT_2/AT_1 ratios. They also produced effective and prolonged antihypertensive effects in renal hypertensive rats following intravenous and oral administration.

The enhancement of AT_2 activity by ortho-substitution is modest, however this effect is important in obtaining balanced affinities. AT_2 enhancement is probably not the result of direct binding of the substituent to the receptor since a variaty of groups give similar effects. That the effect is due solely to hydrogen bonding seems unlikely because an ortho-methyl group also improved AT_2 affinity. Although the reasons for the AT_2 enhancement were not further investigated, we speculate that the ortho-substituent causes a conformational change in the molecule favoring AT_2 binding. Such conformational change could be attributed to steric interaction between the "ortho"-substituent and the R_2 and R_5 groups of the imidazole in the case of the methyl bromo, or nitro groups, or dipole repulsion between the "ortho"-substituent and the R^5 group of the imidazole in the case of the halogen or nitro substituents, or the combination of steric and dipole effect.

A general route to these Ang II antagonists is demonstrated in Scheme I for the preparation of compound **1** and **7**. Imidazole **19**[14] was alkylated with 4-bromo-2-fluorobenzyl bromide (**20**) to yield **21**. Bromobenzyl imidazole **21** was coupled with boronic acid **22**[17] using tetrakis(triphenylphosphine)palladium(0) to produce biphenyl imidazole **23**. Removal of the trityl group with HCl/THF generated the final tetrazole **1**. Bromo-benzyl imidazole **21** was also coupled with boronic acid **24** under the same conditions described above to afford

Table 2. Combination of Ortho-Substitution and Acid Isostere Replacement Effects



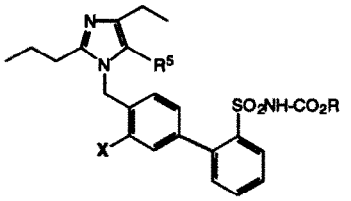
Compd.	R^5	X	[a]IC_{50} (AT_1, nM)	[a]IC_{50} (AT_2, nM)	[b]ED_{30} (mg/kg) *iv; po*
5	CHO	H	2	10	0.23; 0.18
6	"	CH_3	3	9	0.23; 0.86
7	"	F	0.7	2	0.13; <1.0
8	CO_2CH_3	H	2	40	not tested
9	"	NO_2	7	20	not tested
10	"	Br	2	20	not tested
11	"	CH_3	3	10	0.15; 0.56
12	"	Cl	3	7	0.51; 0.44
13	"	F	0.6	4	0.11; <0.3
14	$COCH_3$	H	2	80	0.26; 0.25
15	"	CH_3	2	20	0.24; 0.55
16	"	Cl	6	12	0.11; 0.96
17	"	F	1	3	0.10; 0.48

[a,b]See Table 1 for an explanation of tabluted data.

biphenyl sulfonamide **25**. After the *t*-butyl group was removed, the primary sulfonamide was converted to the carbamate **7** by reaction with *n*-butyl chloroformate. The boronic acids **22** and **24** was prepared by lithiation of either 2-(triphenylmethyl)-5-phenyltetrazole or *N*-*t*-butylbenzenesulfonamide followed by reaction with trimethylborate and hydrolysis of the borate ester.[17,18]

In conclusion, "ortho"-substitution on the biphenyl system enhanced AT_2 affinity. Chloro- and fluoro-substituents produced the best combination of high affinity and balanced AT_1/AT_2 effects in this series. When this ortho-substitution was combined with a sulfonylcarbamate as the acid isostere, balanced AT_1/AT_2 receptor antagonists were obtained. The three best compounds (**12**, **17**, and **18**) exhibited nanomolar affinities for both the AT_1 and AT_2 receptors and possessed a AT_2/AT_1 ratio of less than three. These antagonists showed significant and prolonged antihypertensive effects in renal hypertensive rats following intravenous and oral administration.

Table 3



12: X = Cl; $R^5 = CO_2CH_3$; R = *n*-Bu

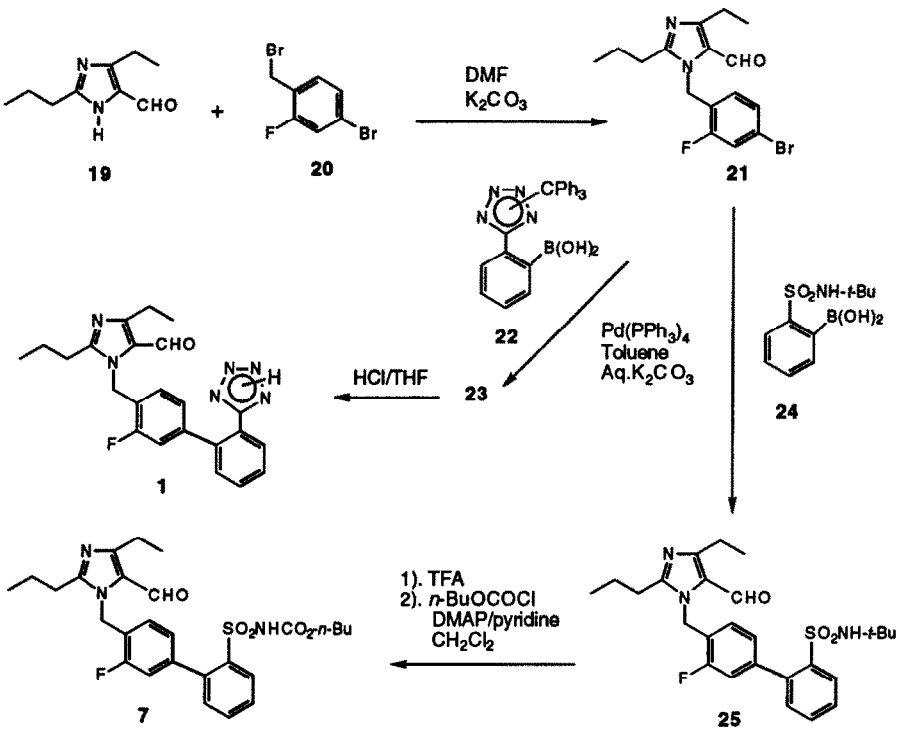
17: X = F; $R^5 = COCH_3$; R = *n*-Bu

18: X =F; $R^5 = CO_2CH_3$; R = *i*-Pen

	Compd.12	Compd.17	Compd.18
IC_{50} (AT_1, nM)[a]	3	1	1
IC_{50} (AT_2, nM)[a]	7	3	1
Ratio of AT_2/AT_1	2.3	3	1
I.V. ED_{30} (mg/kg, RHR)[b]	0.51	0.10	0.12
P.O. ED_{30} (mg/kg, RHR)[b]	0.44	0.48	0.67
Duration (h, RHR)[c]	>24	>24	>24

[a,b]See Table 1 for an explanation of tabluted data.
c. dosed orally at 3 mg/kg.

Scheme I



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