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L-162,389: A POTENT ORALLY ACTIVE ANGIOTENSIN II RECEPTOR ANTAGONIST WITH BALANCED AFFINITY TO BOTH AT_1 AND AT_2 RECEPTOR SUBTYPES.

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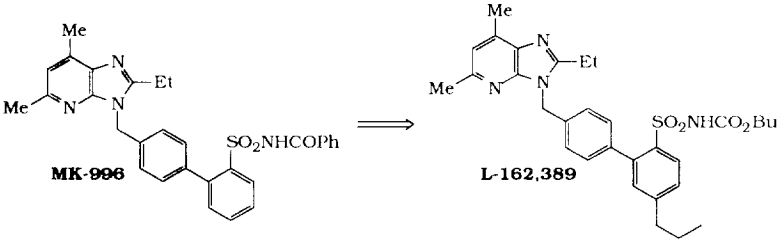
Abstract: Simple modifications made to our potent angiotensin II AT_1 selective clinical candidate MK-996 provided a compound with balanced binding affinity to both the AT_1 and the AT_2 receptor subtype. This compound, L-162,389, is orally active in rats and dogs.



Introduction:

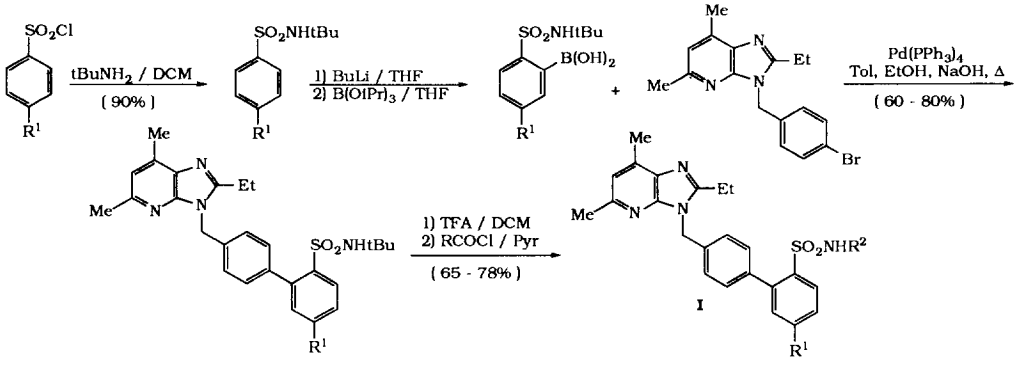
Angiotensin II, the key hormone in the renin-angiotensin cascade, plays a critical role in the regulation of blood pressure and the maintenance of electrolyte balance.[1] The remarkable success achieved by angiotensin converting enzyme inhibitors for the treatment of hypertension and congestive heart failure has generated considerable interest in the development of novel pharmacological agents designed to intervene in the renin-angiotensin system.[2] During the past several years there have been extraordinary advances in the development of potent AT_1 selective nonpeptide angiotensin II receptor antagonists.[3] One such agent, losartan (MK-954), has completed clinical trials and has recently been approved by the FDA.[4] While no side effects were observed during these trials, it was reported that plasma levels of circulating AII were elevated compared to normal.[5] It is expected that these elevated levels of AII would have the potential to stimulate AT_2 receptors. Although the functional response to stimulation of the AT_2 receptor is not yet known, we were interested in developing an antagonist which would inhibit the binding of AII to both receptor subtypes. Our strategy was to build AT_2 binding affinity into our potent orally active AT_1 selective antagonist MK-996.[6] Prior work in our labs had demonstrated that replacement of the benzoylacylsulfonamide acid group ($SO_2NHCOPh$) by a *n*-butyl sulfonyl carbamate (SO_2NHCO_2Bu), in a series of quinazolinones, led to analogs with improved AT_2 binding affinity.[7] We also had previously reported that incorporation of an alkyl group to the 5'-position of the biaryl system increases AT_2 binding affinity in a series of biphenyl triazolinones and phenylthiophene imidazopyridines.[8] The combination of these two modifications to clinical candidate MK-996 resulted in the discovery of L-162,389 (**Ie**), a potent, balanced, and orally active AII antagonist.

Synthesis:

Reaction of *t*-butylamine in dichloromethane with commercially available substituted phenylsulfonyl chlorides (R^1 = H, Me Et, nPr) cleanly afforded the desired corresponding *t*-butylsulfonamides, **1**. Generation

of the dianion with two equivalents of *n*BuLi in THF at -20° C, followed by quench with triisopropylborate afforded the desired phenylsulfonamide boronic acid derivatives (**2**) in good yield after dilute acid work-up. Suzuki coupling of these boronic acids with the 5,7-dimethyl-3-(4-bromobenzyl)-2-ethylimidazopyridine provided the desired biphenyl analogs (**3**) in 60 to 80% yield.[9] The *t*-butyl group was then removed with TFA in dichloromethane and the resultant sufonamide was acylated with an acid chloride or a chloroforamte to provide antagonists **I**.[10]

SYNTHETIC SCHEME



Results and Discussion:

All final compounds (**I**) competitively blocked the specific binding of the radioligand ^{125}I[Sar^1,Ile^8]AII to a rabbit aorta (for the AT_1 receptor) and a rat midbrain (for the AT_2 receptor) membrane preparation with IC_{50}'s as listed in the table below.[11] A 30-fold increase in the AT_2 binding affinity was observed when the benzoylacylsulfonamide acid moiety found in MK-996 was replaced by a *n*-butylsulfonyl carbamate group. Addition of a methyl at the 5'-position had little effect on binding affinity at either the AT_1 or the AT_2 receptor. However, addition of an ethyl and finally a propyl group did have a significant impact on binding affinities, compounds **Id** and **Ie**, respectively. This increase in affinity toward the AT_2 receptor was also accompanied by a attenuation of affinity toward the AT_1 receptor in both examples, however the combined binding affinities of **Ie** certainly met the criteria (AT_2/AT_1 IC_{50} ratios of ≥ 2) set for further development of a balanced antagonist. Compound **Ie** also had good balanced potency in our human receptor assay elliciting IC_{50}'s of 7 nM and 17 nM in the human adrenal AT_1 and AT_2 receptor assay, respectively.[12]

IC_{50} Binding Affinities

Compound	R^1	R^2	AT_1 affinity	AT_2 affinity
Ia (MK-996)	H	COPh	0.2 nM	2900 nM
Ib	H	CO_2nBu	0.2 nM	95 nM
Ic	Me	CO_2nBu	0.2 nM	87 nM
Id	Et	CO_2nBu	1.4 nM	37 nM
Ie	nPr	CO_2nBu	2.1 nM	3.8 nM

Compound **Ie**, the 5'-n-propyl analog, was further evaluated intravenously and orally in our conscious rat and dog pressor response assay. The results from these experiments are graphically illustrated in Figures 1 and 2, respectively.

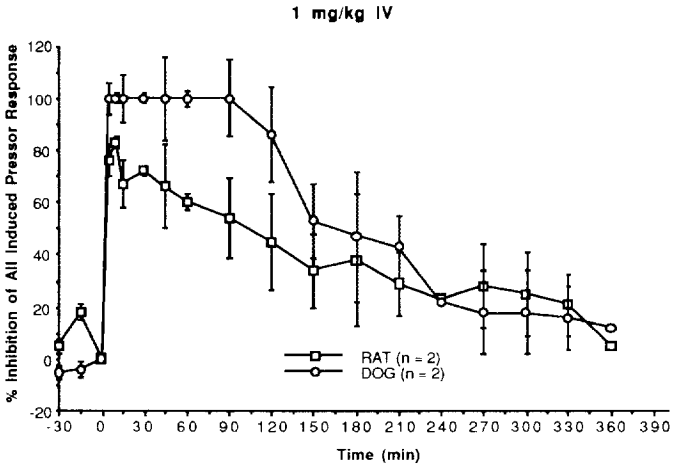


Figure 1: A comparison of the duration of action of compound **Ie** in conscious rats (open squares) and normotensive dogs (open circles) at 1 mg/kg iv. The pressor responses to AII were measured in each animal after receiving a single dose of **Ie**. The animals were challenged with 0.1 μg/kg of AII at specific time intervals.

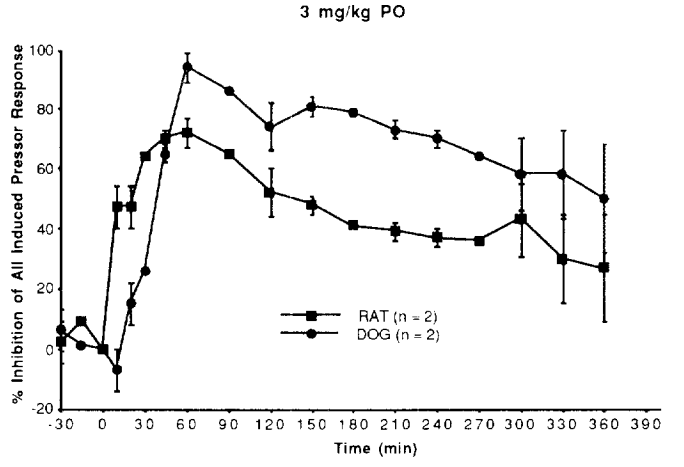


Figure 2: A comparison of the duration of action of compound **Ie** in conscious rats (closed squares) and normotensive dogs (closed circles) at 3 mg/kg po. The pressor responses to AII were measured in each animal after receiving a single dose of **Ie**. The animals were challenged with 0.1 μg/kg of AII at specific time intervals.

Summary:

We have described alterations to our AT_1 selective clinical candidate MK-996 which provided a potent balanced affinity ligand to both the AT_1 and AT_2 receptors. This balanced antagonist, L-162,389, inhibited the pressor response due to exogenously administered AII in conscious normotensive rats and dogs. At 1

mg/kg i.v in rats L-162,389 showed 85% peak inhibition with a duration of 3 hours. In dogs the same dose resulted in a peak inhibition of 100% with a duration of 4 hours. Orally at 3 mg/kg, a peak inhibition of 70% and 92% was observed with duration of of 5-6 hours, in rats and dogs respectively.

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9. The structure assigned to each new compound is in accord with its mass spectrum (FAB) and high field ^1H NMR (400 MHz).

10. Final products were characterized by mass spectrum (FAB), high field ^1H NMR (400 MHz), and combustion analysis (C, H, N; within ± 0.4% of theoretical values).

11. For assay details see: (a) Chang, R. S. L.; Siegl, P. K. S.; Clineschmidt, B. V.; Mantlo, N. B.; Chakravarty, P. K.; Greenlee, W. J.; Patchett, A. A.; Lotti, V. J. *Pharmacol. Exp. Ther.* **1992**, *262*,133. (b) Chang, R. S. L.; Lotti, V. J.; Faust, K. A. *Biochem. Biophys. Res. Commun.* **1990**, *171*, 813.

12. Since both AT_1 and AT_2 receptors are present in human adrenal tissues, IC_{50} values on AT_1 and AT_2 were determined in the presence of 1 μM PD121981 (AT_2 selective ligand) or losartan to prevent binding to the AT_2 and AT_1 receptors, repectively.

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