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SUBSTITUTED LACTAM BIPHENYLTETRAZOLES AS ANGIOTENSIN II MEDIATED ANTIHYPERTENSIVES

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Abstract: A novel series of biphenyltetrazololactams has been identified as potent angiotensin receptor antagonists. These compounds were then evaluated in two in vivo preparations to determine their oral efficacy as antihypertensives. From these preparations RWJ 46458, **9**, was identified as a lead compound and subjected to secondary evaluation.

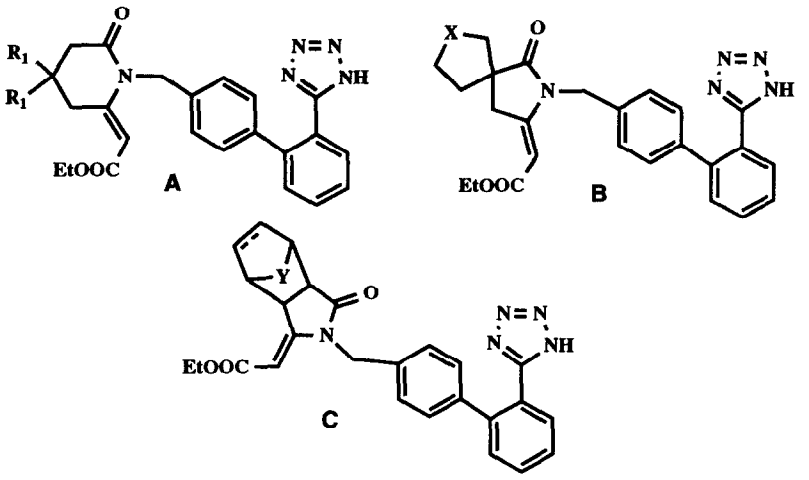
Control of hypertension with angiotensin II (AII) receptor antagonists has been an area of vigorous research in the last five years. Losartan, the most clinically advanced AII antagonist, has proven to be a potent AII antagonist as well as a potent long acting antihypertensive agent.[1] We have previously described in vitro structure activity relationships of two series of lactam AII antagonists.[2] Herein we will describe the in vivo structure activity relationships of both of these series as well as some additional profiling of our lead compound, RWJ 46458 (**9**). In Table 1, the structures of these lactams are described along with their pA_2 values.

In the in vivo studies of these series, we have utilized two test systems to evaluate compounds for oral antihypertensive activity. The first of these preparations is a sodium depleted normotensive rat preparation.[3] This preparation increases plasma renin levels and is well suited to measuring the hypotensive effects of AII specific antagonists. In Table 2, oral in vivo data on a number of lactam biphenyltetrazoles tested in this preparation are reported. The maximum blood pressure response in this preparation is a drop of ~35 mm Hg and activity is expressed as a percentage of maximal blood pressure drop.[4] In the high renin rat, a number of compounds show activity at the screening dose of 30 mg/kg. Compounds **6** of series B and **7** of series C are moderately active, but **9** is clearly the most potent compound in this model. Compound **9** also shows a more rapid onset of action than losartan, indicating that metabolic activation may not be needed. It is interesting that both **6** and **9** are also the most potent compounds in our in vitro rabbit aortic ring preparation.[5] Compound **7**, however, is less potent in vitro than compound **4**. We believe that the better in vivo activity may be due to reduced ring strain in the molecule. The ring strain could potentially increase the rate at which the 5-membered lactam is hydrolyzed and deactivated.

The second oral screening model we utilized is the spontaneously hypertensive rat (SHR).[7] The SHR is a preparation which more closely approximates human essential hypertension. Antagonists of the renin angiotensin system produce a maximal decline of ~45mm Hg in this preparation and our data are presented as percentages of maximum response.[8] As our AII SAR evolved we used the SHR as our primary oral in vivo test system.

As we noted in the high renin rat model, **9** is our most potent compound at the screening dose of 30 mg/kg. Compounds **6** and **7** again show activity as in the high renin rat, but a less strained tricycle (**18**) was now found to

Table 1



A	R_1	R_2	pA_2
1	Me	Me	7.4
8	spirocyclopentane		7.9
9	Me	Et	9.0
10	Et	nPr	7.9
11 (methylester)	Et	Et	8.4
12	Et	nBu	7.0
13 (methylester)	Me	Et	8.6
14	Me	iPr	7.8
15	Me	nBu	7.5
16	Et	Et	8.1
17	spirocyclohexyl		8.3

B	X	pA_2
2	CH_2	8.5
3	$(CH_2)_2$	7.9
6	$(CH_2)_3$	8.4

C	Y	saturation	pA_2
4	CH_2	+	9.0
5	$(CH_2)_2$	-	8.2
7	$(CH_2)_2$	+	8.0
18	$(CH_2)_3$	+	7.7
losartan			8.8

be the most potent member of the tricyclic series (structure C). A number of additional piperidine derivatives (structure A) were also found to be potent antihypertensives in this preparation. Compounds **15**, **16** and **17** all gave a maximal blood pressure response at the screening dose. All of these compounds also had a rapid onset of action. In addition, compounds **9**, **15**, **16**, and **18** all had durations of at least 24 hours. We reduced the doses in the SHR (3 and 10 mg/kg) and identified **9**, RWJ 46458, as our most potent compound in our in vitro and in vivo preparations.

In our rabbit aortic rings assay we found **9** to be an insurmountable antagonist of AII (Fig. 1) and not to inhibit either phenylephrine or KCl induced contraction in rabbit aortal rings indicating specificity for AII. We studied **9** in an additional functional assay which measures AII induced secretion of aldosterone from rat adrenal cortical cells. In the adrenal assay we found **9**, over the concentration range of 10 to 1000 nM, caused a parallel rightward shift of

Table 2

High Renin Rat [6] (30 mg/kg po)

#	% Max Drop MAP	Onset (hours)	Duration (hours)
1	17	2	5
2	20	2	3
3	26	1	17
4	26	1	17
5	29	1.75	17
6	31	0.75	23
7	43	0.25	10
8	46	2.5	21
9	100	0.25	<24
losartan	100	2	22

Table 3

Spontaneously Hypertensive Rat[9] (30 mg/kg po)

#	% Max Drop MAP	Onset (hours)	Duration (Hours)
6	80	1.5	16
7	86	1	13
9	100	0.25	24
10	18	3	6
11	35	0.75	15
12	55	0.25	8
13	58	0.5	16
14	70	1.25	5
15	98	0.5	24
16	100	0.25	24
17	100	0.25	8
18	96	0.25	24
losartan	100	2	24

the angiotensin II dose response curve (Fig. 2). Based on the concentrations used and the magnitude of the shift, it appears that **9** is about equipotent to losartan in antagonizing angiotensin II-induced aldosterone secretion (Fig 3) and, like losartan, is a competitive antagonist. Saralasin also caused a parallel shift to the right in the dose response curve, indicating antagonism at the angiotensin II receptor. However, the maximum response was suppressed, suggesting non-competitive inhibition.

Compound **9** was evaluated for antagonism of AII induced pressor responses in ganglion-blocked rats. It was found to shift the vasopressor dose response curve to the right in a competitive manner. It was also found to be about equivalent in potency to losartan in this i.v. preparation (Fig 4). Compound **9** causes graded reductions in mean arterial pressure in the SHR after i.v. administration of 3 and 10 mg/kg (Fig. 5). The antihypertensive effect

has a rapid onset and is not accompanied by reflex tachicardia (Fig 6). We observe dose related reductions in bloodpressure (po) in both the salt depleted rat (Fig 7) and the SHR (Fig 8). Finally, **9** reduces both systolic and diastolic pressure without compensatory tachycardia or tolerance after chronic (7 day) treatment in the SHR.

In conclusion, compound **9**, RWJ 46458, is a specific orally active AII antagonist which has potential in treating hypertension and other angiotensin-dependent pathology.

Fig. 1

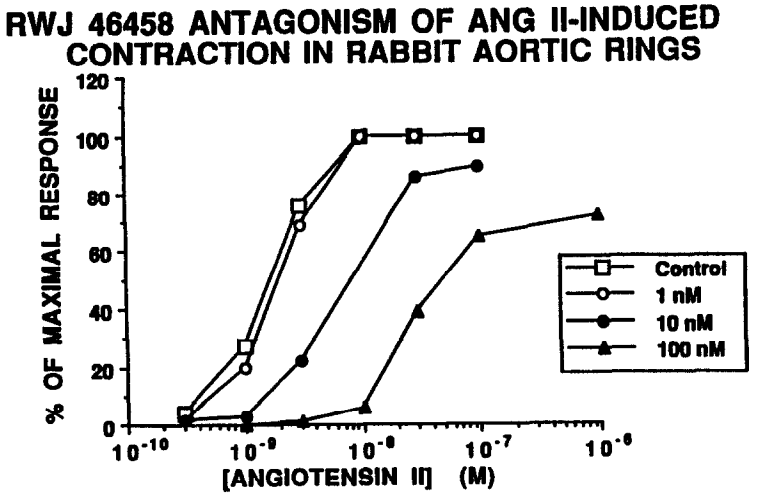


Fig. 2

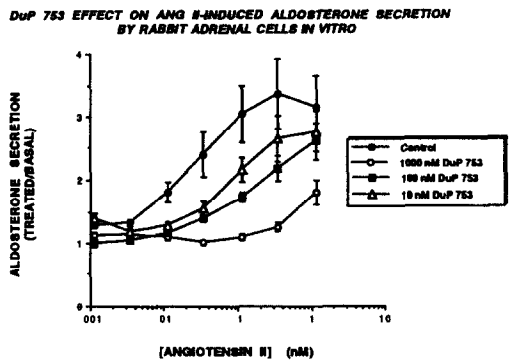


Fig. 3

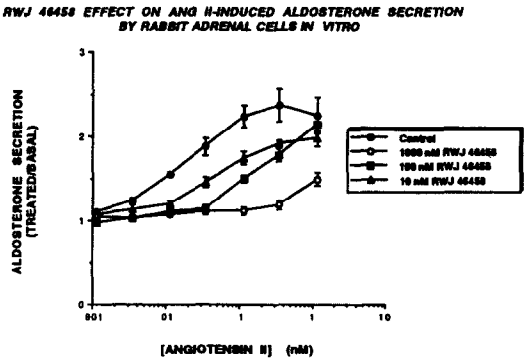


Fig. 4

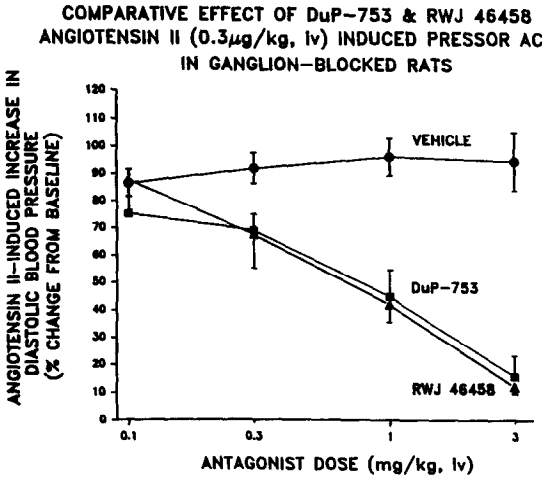


Fig. 5

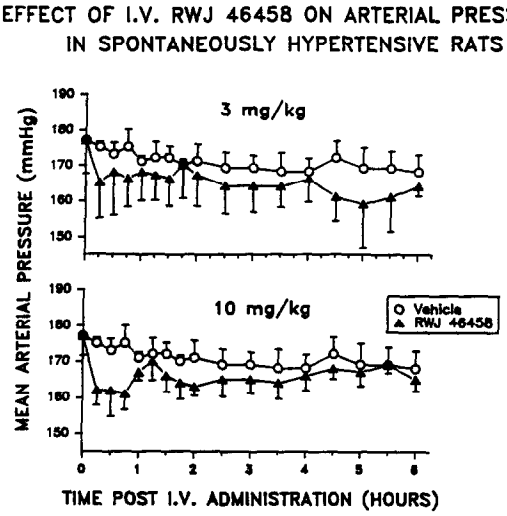


Fig. 6

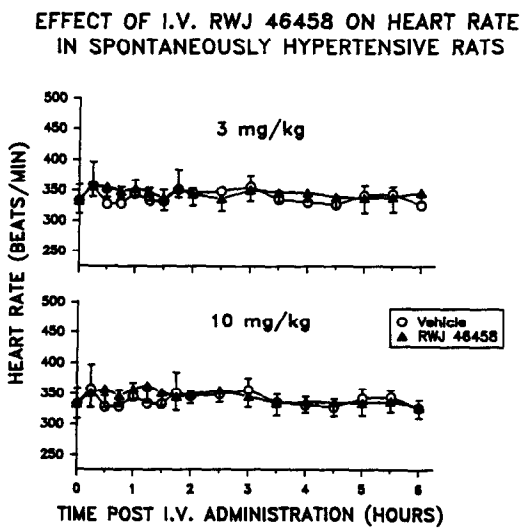


Fig. 7

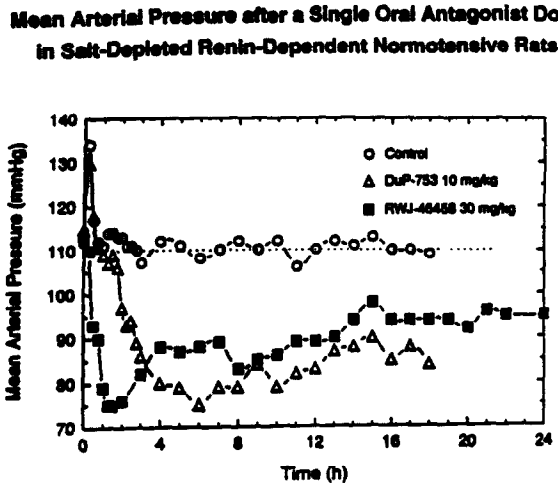
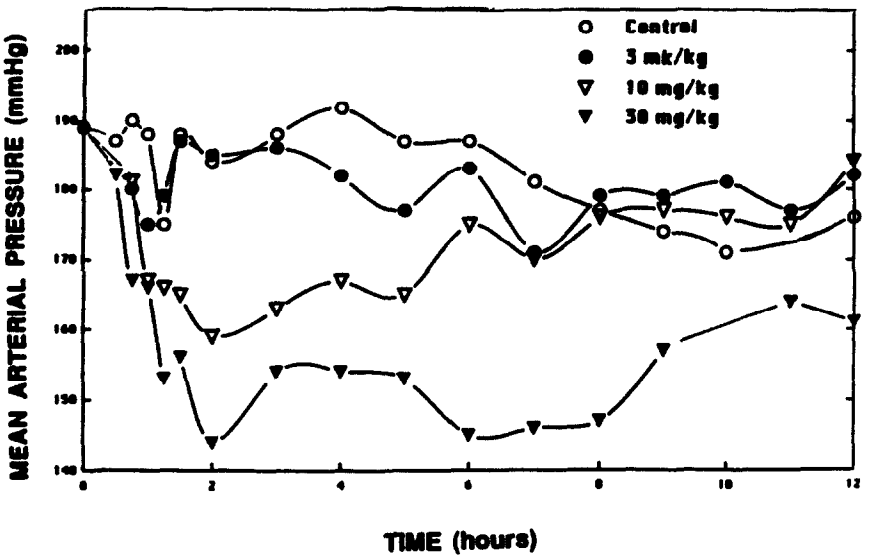


Fig 8 EFFECT OF RWJ 46458 ON MEAN ARTERIAL PRESSURE IN SHR AFTER ORAL ADMINISTRATION



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4. Maximal dose is determined by treating the animals with excess enalapril or losartan.
5. See reference 2 for procedures.
6. Compounds tested as their pyridinium salts.
7. Okamoto, K., Aoki, K. *Jpn. Circ. J.* **1963**, *27*, 282.
8. Maximal dose is determined by treating the animals with excess enalapril or losartan.
9. Compounds tested as their pyridinium salts.
10. In each preparation (Fig. 4 through 8), 3 animals per dose were used.

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