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IMIDAZOLINONES AS NONPEPTIDE ANGIOTENSIN II RECEPTOR ANTAGONISTS

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Abstract: A series of biphenyl imidazolinones were synthesized as nonpeptide angiotensin II receptor antagonists. While those compounds with a tetrazole functionality were found to be AT_1 selective, those with a sulfonamide moiety showed affinities for both the AT_1 and the AT_2 sites. Representative compounds were very active in lowering blood pressure in conscious renal hypertensive rats following intravenous administration.

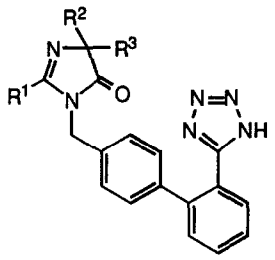
The renin-angiotensin system (RAS) plays an important role in blood pressure regulation. Angiotensin II (Ang II) is the biologically active component of the RAS responsible for the peripheral effects of this system. The potential role for Ang II receptor antagonists in the treatment of hypertension has been well documented and exemplified by Cozaar® (losartan, DuP 753).[1] The discovery of Cozaar® has led to fruitful research activity in the pharmaceutical industry in the Ang II area.[2] There is evidence that there are at least two Ang II receptor subtypes designated as AT_1 and AT_2.[3] Losartan is selective for the AT_1 site which mediates most of the known Ang II physiologic functions. The functions of the AT_2 site are unclear at this time, however AT_2 receptor mediated effects of Ang II have been proposed.[4]

Recently Bernhart et al.[5] reported some imidazolinones with selective affinity for the AT_1 receptor site. We have also synthesized a series of biphenyl imidazolinones. Those compounds with a tetrazole moiety as the acidic functionality showed selective affinity for the AT_1 site as observed by Bernhart.[5] In addition, we have prepared some imidazolinones with affinities for both the AT_1 and AT_2 receptors.

The binding affinities and antihypertensive effects of these biphenyl tetrazolyl imidazolinones are shown in Table 1. Alkyl is preferred over aryl for R^1, R^2 and R^3. A 14-fold increase in affinity was observed when R^1 was changed from phenyl to methyl (**Ex.1** and **Ex.2**); a 75-fold increase in affinity was obtained when R^2 and R^3 were both changed from phenyl to methyl (**Ex.3** and **Ex.5**). The spiro-compounds (**Ex.6-11**) showed nanomolar binding affinity. Most of these compounds were very active in lowering blood pressure in conscious renal hypertensive rats following intravenous administration as indicated in Table 1.[7] All of these compounds have an IC_{50} greater than 10,000 nM for the AT_2 site.

Acyl sulfonamides were described by the Merck group[8] as a replacement for the tetrazole moiety, and for this acid functionality it was found that the AT_2 affinity was enhanced in comparison to the tetrazole analogs. Several acyl sulfonamides were synthesized in this series and are reported in Table 2. While the AT_1 affinity remained in the nanomolar range, the AT_2 affinity was indeed improved. **Ex.12** and **Ex.13** showed a 50-fold

Table 1. Binding Affinities and Antihypertensive Activities of Biphenyl Tetrazolyl Imidazolinones



Ex. No.	R^1	R^2, R^3	IC_{50} (AT_1, nM)[a,b]	ED_{30} (mg/kg) i.v.[c]
1	phenyl	Ph, Ph	1400	not tested
2	methyl	Ph, Ph	100	not tested
3	*n*-propyl	Ph, Ph	300	not tested
4	*n*-propyl	CF_3, CF_3	20	not tested
5	*n*-propyl	CH_3, CH_3	4	0.36
6	*n*-propyl	$-(CH_2)_2-$	3	0.54
7	*n*-propyl	$-(CH_2)_4-$	0.9	0.32
8[d]	*n*-butyl	$-(CH_2)_4-$	0.9	0.16
9	*n*-propyl	$-(CH_2)_5-$	3	0.25
10	*n*-propyl	$-(CH_2)_2-S-(CH_2)_2-$	2	0.26
11	*n*-propyl	$-(CH_2)_2-O-(CH_2)_2-$	8	0.20

a. Inhibitory concentration of potential Ang II antagonists which gave 50% displacement of the total specifically bound[^{125}I] Ang II [6]

b. IC_{50} 's for the AT_2 receptor are greater than 10,000 nM for all these compounds.

c. Effective dose to lower blood pressure by 30 mm Hg in renal hypertensive rats (RHR)[7].

d. Reported by Bernhart. see reference 5.

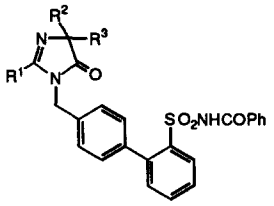
increase in AT_2 affinity over the corresponding tetrazoles (**Ex.5** and **Ex.10**). A 100-fold increase in AT_2 affinity was observed for **Ex.15** relative to **Ex.8**. These compounds also produced a significant antihypertensive effect in renal hypertensive rats when administrated intravenously as shown in Table 2.

The sulfonamides were prepared by a similar method to that described by Naylor et al.[8] as outlined in Scheme I. Benzenesulfonyl chloride **16** was reacted with *t*-butyl amine to give N-*t*-butylbenzensulfonamide. The benzenesufonamide was lithiated followed by reaction with trimethyl borate and hydrolysis to yield boronic acid **17**. Palladium-catalyzed coupling of boronic acid **17** with *p*-bromotoluene gave biphenyl **18**. Reaction of **18** with NBS/AIBN yielded benzyl bromide **19**. Alkylation of imidazolinone **20**[5a] with **19** produced biphenyl imidazolinone **21**. After the *t*-butyl protecting group was removed, the primary sulfonamide was coupled with

benzoic acid to give the sulfonamide **12.**

In conclusion, we have synthesized a series of imidazolinones as nonpeptide angiotensin II receptor antagonists. When the tetrazole moiety was used as the acid isostere, the imidazolinones were selective for the AT_1 site; when the acyl sulfonamide was used, the AT_2 affinities were significantly enhanced. Both the tetrazoles and sulfonamides were very active in lowering blood pressure in renal hypertensive rats following intravenous administration.

Table 2. Binding Affinities and Antihypertensive Activities of Acyl Sulfonamides

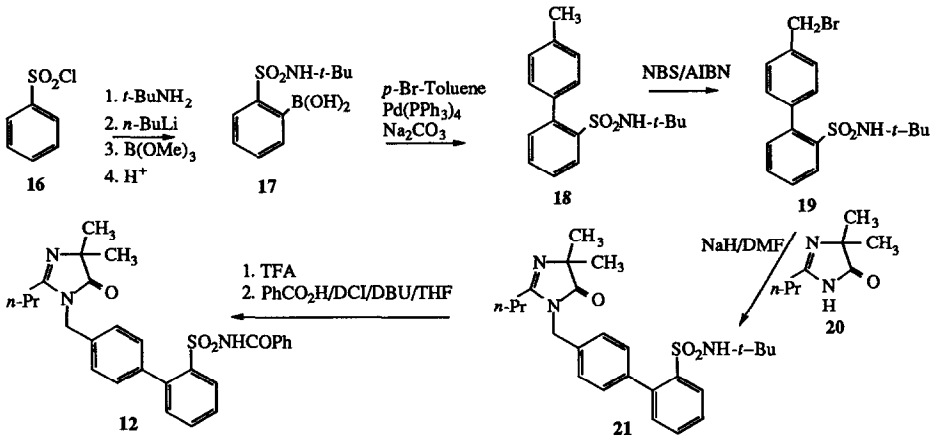


Ex.. No.	R^1	R^2R^3	IC_{50} (AT_1;AT_2, nM)[a]	ED_{30}(mg/kg) i.v.[b]
12	*n*-propyl	CH_3, CH_3	3; 200	0.17
13	*n*-propyl	-$(CH_2)_2S(CH_2)_2$-	1; 200	0.29
14	*n*-propyl	-$(CH_2)_4$-	9; 300	0.14
15	*n*-butyl	-$(CH_2)_4$-	1; 100	0.29

a. Inhibitory concentration of potential Ang II antagonists which gave 50% displacement of the total specifically bound[^{125}I] Ang II [3a, 6]

b.Effective dose to lower blood pressure by 30 mmHg in renal hypertensive rats (RHR)[7].

Scheme I



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