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DEVELOPMENT OF TETRAZOLE BIOISOSTERES IN ANGIOTENSIN II ANTAGONISTS

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Abstract: The application of acidic heterocycles as a substitute for tetrazole in the synthesis of potent non-peptide Angiotensin II AT1 receptor antagonists is described.

Since the discovery of the first non-peptide Angiotensin II (AII) receptor antagonist DuP 753 - (Losartan)[1] a series of non-peptides has been described. In Losartan and in most of these compounds, the biphenyl tetrazole moiety was necessary to obtain the greatest potency and bioavailability. Although tetrazole was replaced by a variety of isosteres of varying structure and acidity[1,2] none of the synthesized compounds showed the same or a better activity than those with tetrazole.

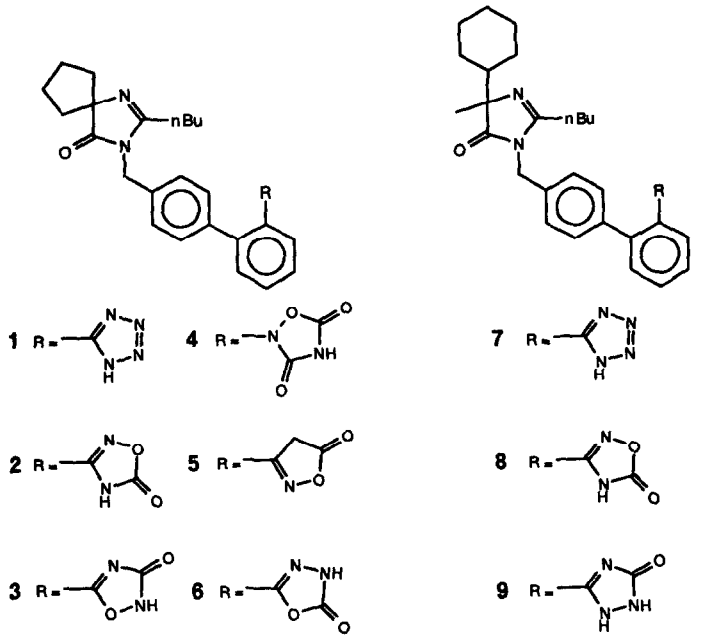


Table I

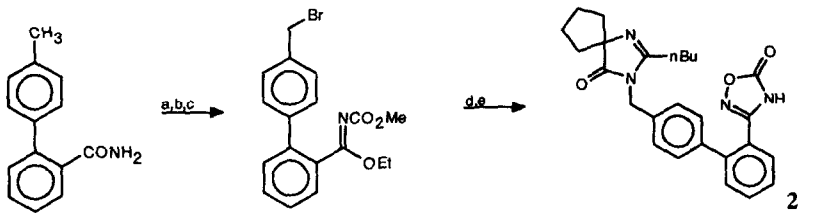
Starting from the structure of Losartan, we describe a new series of potent antagonists. In these compounds the imidazole ring was replaced by the dihydro-imidazol-4-one structure. Compound **1** (SR 47436)[3-5] bearing in position 5 a spirocyclopentane ring, was 10 times more active than DuP 753 and is for the moment undergoing Phase II clinical trials.

Compounds bearing in position 5 both cycloalkyl and alkyl subtituents were also potent AII antagonists[6,7]. In this series, the most active compound was dextrorotatory cyclohexyl-methyl **7**.

In order to produce non-tetrazole analogues with greater potency and bioavailability, several compounds having the biphenyl moiety substituted with different heterocyclic five membered rings were synthesized[8]. We focused on planar acid moieties and more particularly on oxazolone, oxadiazolone and triazolone derivatives.

The imidazolinone AII antagonists containing these acid mimics are summarized in Table I and their syntheses are described in schemes 1-6, according to referenced procedures.

Scheme 1: 1,2,4-Oxadiazol-5-one[9]



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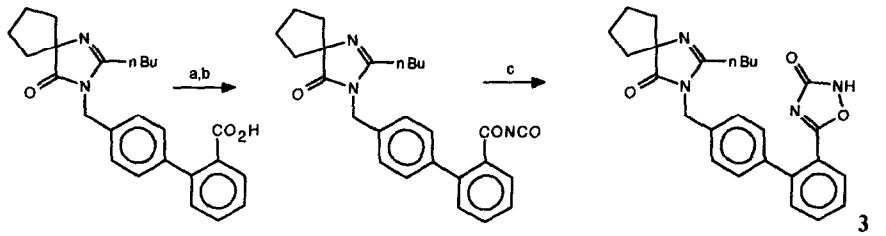
a) $Et_3O^+PF_6^-/CH_2Cl_2$ b)$ClCO_2Me$/2,4,6-Trimethylpyridine/Hexane-Reflux
c) NBS/AIBN/CCl_4-Reflux d) Dihydro-Imidazol-4-one/NaH/DMF
e) NH_2OH/MeOH-Reflux

Scheme 2: 1,2,4-Oxadiazol-2-one[10]



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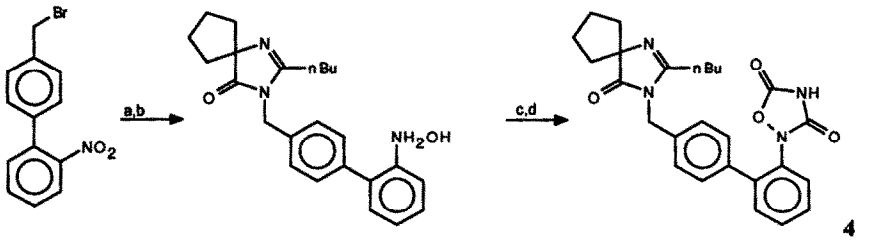
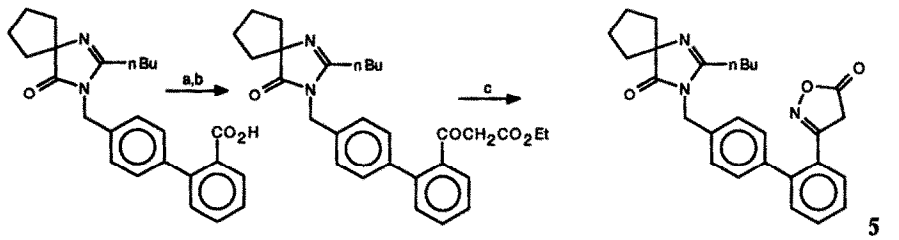
a) NH_4OH/BOP/dioxane b)ClCOCOCl/$ClCH_2CH_2Cl$-Reflux
c) N_3SiMe_3/Xylene-Heat

Scheme 3: 1,2,4-Oxadiazolidine-3,5-dione[11]



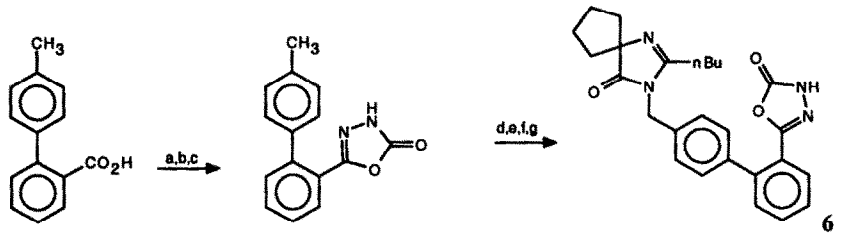
a) Dihydro-Imidazole-4-one/NaH/DMF b) Zn/NH_4Cl/Dioxane/H_2O
c) $OCN\text{-}CO_2Et/CH_2Cl_2$ d) TritonB/MeOH-Reflux

Scheme 4: Isoxazol-5-one[12]



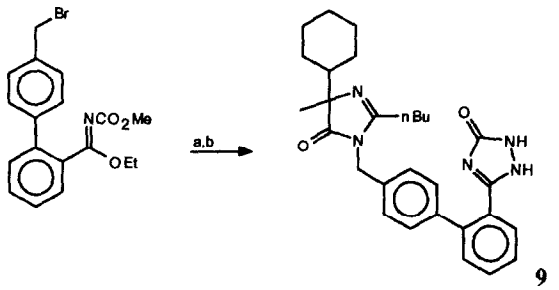
a)$SOCl_2/CH_2Cl_2$ b) $EtO_2C\ CH_2CO_2H$/BuLi,-70°C c) NH_2OH/Pyridine

Scheme 5: 1,3,4-Oxadiazol-2-one[13]



a) $ClCOCOCl/CH_2Cl_2$ b) H_2NNH_2/THF c) $COCl_2/CHCl_3$-Reflux d) Ph_3CCl/CH_2Cl_2/TEA
e) NBS/$(PhCO_2)_2/CCl_4$-Reflux f) Dihydro-Imidazol-4-one/NaH/DMF g) HCO_2H/H_2SO_4

Scheme 6: 1,2,4-Triazol-3-one [9]



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a) Dihydro-Imidazol-4-one/NaH/DMF b) H_2N-NH_2/MeOH-Reflux

It was not easy to establish a direct relationship between acidity and affinity. In this series, however, it may be that the geometry and/or charge distribution around the acid mimic were important factors for receptor interaction. All these heterocyclic rings present a tautomeric behaviour ; the proportion of each form in solution[14,15] and the structure of the real active tautomer were difficult to appreciate.

The compounds reported were tested for competitive inhibition of AII binding using rat liver membrane preparations and their antagonistic properties were assessed through the inhibition of the AII-induced contractions of rabbit aortic strips.

As summarized in Tables II and III, the binding affinities of compounds 2 and 8 bearing the 1, 2, 4-Oxadiazol-5-one and compound 4 bearing the 1, 2, 4-Oxadiazolidine-3,5-dione were similar to those of the tetrazole parent.

Table II: 5-Spirocyclopentyl-dihydro-Imidazol-4-one AII antagonists

Compound	Binding IC_{50}[a], nM	Rabbit aortic ring IC_{50}[b], nM
1 (SR 47436)	1.3	4.0
2	1.7	2.6
3	230	-
4	1.4	2.8
5	25	140
6	60	67
DuP 753	14	26.4

a) Inhibition of specific binding of [^{125}I] Angiotensin II (0.1 nM) on rat liver membranes[5]
b) Inhibition of the contractile response to Angiotensin II (10 nM) of rabbit aortic rings[5]

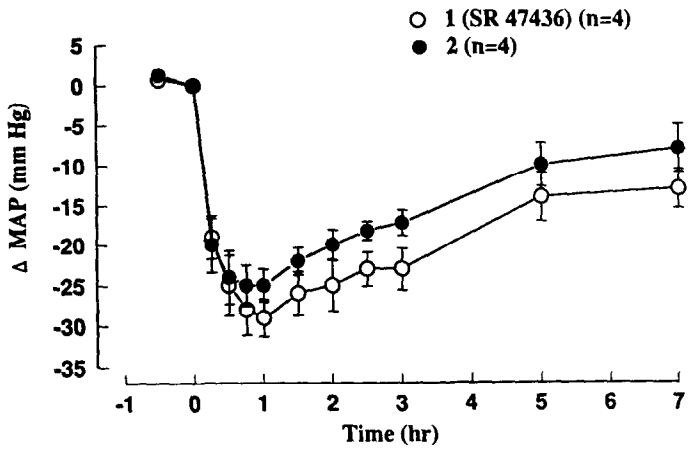
Table III: 5-cyclohexyl-5-methyl-dihydro-Imidazol-4-one AII antagonists

Compound	Binding IC_{50}[a], nM	Rabbit aortic ring IC_{50}[b], nM
7[c]	5.2	0.77
8[c]	0.7	0.64
9[d]	100	

a), b) See legend in Table II for an explanation of tabulated data
c) Dextrogyre enantiomer d) racemic

These compounds were further tested for oral activity in normotensive cynomolgus monkeys. Compound 4 reduces AII-induced pressor response after oral administration (45 % at 3 mg/kg vs. 85 % for SR 47 436 in the same conditions). In sodium-depleted cynomolgus monkeys compound 2 was approximatively equipotent to SR 47436 as shown in Fig. 1.

Fig. 1: Hypotensive effects of compounds 1 and 2 at 3 mg/kg p.o. in sodium-depleted cynomolgus monkeys.



Conclusion:

In this paper we describe some derivatives of the original imidazolinone structure bearing heterocycles as potential bioisosteres of the tetrazole moiety. Two of these heterocyclic moieties are valuable substituents for tetrazole in dihydro-imidazole-4-one series but also in other AII antagonist series. As their synthesis avoids the use of hazardous tin and azide derivatives, these compounds might be useful candidates for further development.

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