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DISCOVERY OF NONPEPTIDE, POTENT CONFORMATIONALLY RESTRICTED ANGIOTENSIN II RECEPTOR ANTAGONISTS

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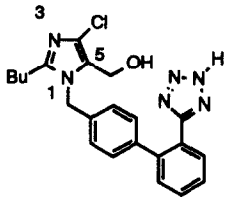
Abstract: A series of potent, selective, conformationally restricted angiotensin II (AII) receptor antagonists has been discovered. Two classes of conformationally restricted analogues were prepared: triazolone-based and imidazole-based biphenyl derivatives. The most active compound, an imidazole-based analogue, has an IC_{50} of 11 nM and a pA_2 of 8.8.

The renin-angiotensin system plays a fundamental role in blood pressure, fluid and electrolyte homeostasis. Angiotensin II receptor antagonists, angiotensin converting enzyme (ACE) inhibitors[1] and renin inhibitors[2] have all been used to investigate the involvement of the renin-angiotensin system in essential hypertension. Due to the side effects associated with ACE inhibitor therapy in some patients, including persistent cough and angioedema,[3] the control of high blood pressure with selective, nonpeptidic AII receptor antagonists has become one of the most intensively studied therapeutic treatments in recent years.[4,5,6]

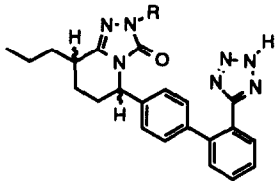
No potent, rigid AII antagonists have been reported thus far.[7] Moreover, since most of the AII antagonists which have been reported are based on DuP 753 (**1**), which features a flexible biphenylmethyl moiety, it has been very difficult to predict the active conformation of these analogues in the binding site. Although several groups have used molecular modelling techniques to reduce the number of possible active conformations, the answer nonetheless remains elusive.[8] We believe that the discovery of potent and selective conformationally restricted AII antagonists could shed light on the active conformations of AII antagonists and possibly that of angiotensin II at the ligand binding site. This knowledge eventually may contribute to an understanding of the mechanism of angiotensin II agonist action at the receptor. Despite the high risk of failure generally associated with the conformation-restriction approach, the scientific significance of the discovery of a potent, conformationally restricted AII antagonist and the potential capability to design more potent, selective antagonists based on such a discovery made our investigation worthwhile.

Compounds **2** and **3** were chosen as our initial target molecules. Both compounds have a linker tethering the heterocyclic ring to the methylene group of the biphenylmethyl moiety. Conformational analysis of these molecules using hand-held molecular models suggested that the biphenyl moiety exists in two low

energy conformations: the axial and equatorial (in the six-membered linker ring). The biphenyl group in the axial conformation is orthogonal to the heterocyclic ring, whereas in its equatorial conformation it will orient toward either the right side of the molecule (for compound **2**) or the left (for compound **3**).



1, DuP 753



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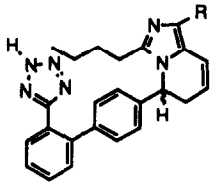

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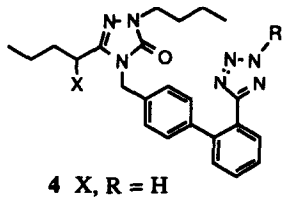
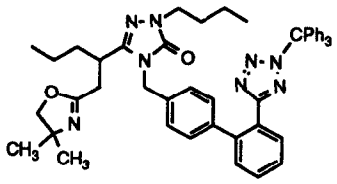
Scheme I[a]



4 X, R = H
a **5** X = H, R = CPh_3
6 X = Br, R = CPh_3

b



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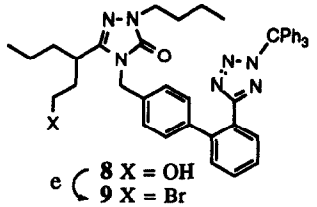
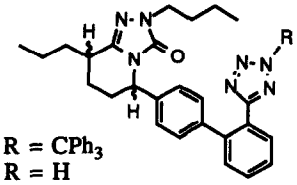
c,d



e **8** X = OH
9 X = Br

f



g **10**, **11** R = CPh_3
12, **13** R = H

[a] **Reagents**: (a) NBS, AIBN, CCl_4, (61%); (b) 2,4,4-trimethyl oxazoline, LDA, THF (65%); (c) MeI, CH_3CN; (d) $NaBH_4$, CH_3OH; followed by NH_4Cl (aq), then more $NaBH_4$ (66%); (e) CBr_4, PPh_3 (85%); (f) LDA, THF, -78 °C (88%); (g) 10% water in acetic acid (85%).

As shown in Scheme I, analogues of compound **2** were prepared from compound **5**.[6b] The trityl-deprotected free tetrazole, compound **4**, has an IC_{50} value[9] of 5 nM, and is a potent, orally active AII antagonist with long duration of action.[6f] Radical-initiated bromination of **5** with NBS selectively brominated the sidechain at the 2-position. The resulting bromide **6** was treated with 2-lithiomethyl-4,4-dimethyl oxazoline to give **7**, which was reduced and subsequently hydrolyzed to the corresponding aldehyde.

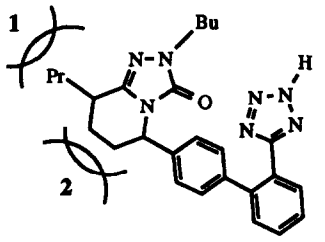
Reduction with $NaBH_4$ gave the alcohol **8** which was converted to the bromide **9** with Ph_3P and CBr_4. Deprotonation of the benzylic methylene proton with LDA followed by subsequent ring-closure gave a 1:1 mixture of two separable stereoisomers **10** and **11**, which were subjected to detritylation conditions with wet acetic acid to give the conformationally restricted triazolones as two racemic pairs of *trans* - and *cis*-isomers, **12** and **13** (IC_{50} = 1,800 and 1,600 nM). The stereochemistry was not assigned at this point. Comparing the IC_{50}s of these two conformationally restricted analogues with the flexible parent compound **4**, it was found that the structural modification to lock the conformation of the molecule caused a 300-fold decrease in the binding affinities (or 150-fold decrease assuming only one enantiomer was active).

There are several structural changes which may have caused the dramatic decrease in the binding affinities of these conformationally restricted analogues. One would have to rule out these possibilities before concluding that the conformations of these two compounds were not the active conformations (see Figure 1):

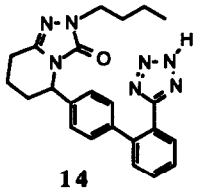
1. The orientation of the propyl sidechain was fixed and might not be able to adopt the conformation needed to fit into the primary lipophilic pocket. Furthermore, it may cause severe unfavorable steric interactions with the receptor.

2.The ethyl linker which was designed to introduce rigidity into the molecule by tying together the biphenyl moiety with the 5-butyl sidechain may be sterically unfavorable.

Fig. 1. Possible Steric Interactions of Conformationally Restricted Antagonists with the Receptor.



First, an analogue without the propyl sidechain **14**, prepared via a similar synthetic route as Scheme I, had a binding affinity 10-fold lower than **12** or **13**. This result argues against the first explanation for the loss in potency, and furthermore suggests that the butyl sidechain in the flexible parent compound may also have oriented in the same direction as in the conformationally restricted analogue.



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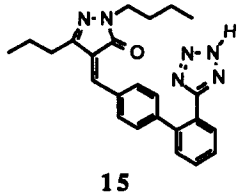

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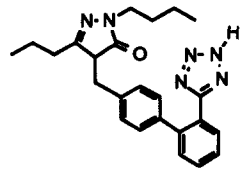


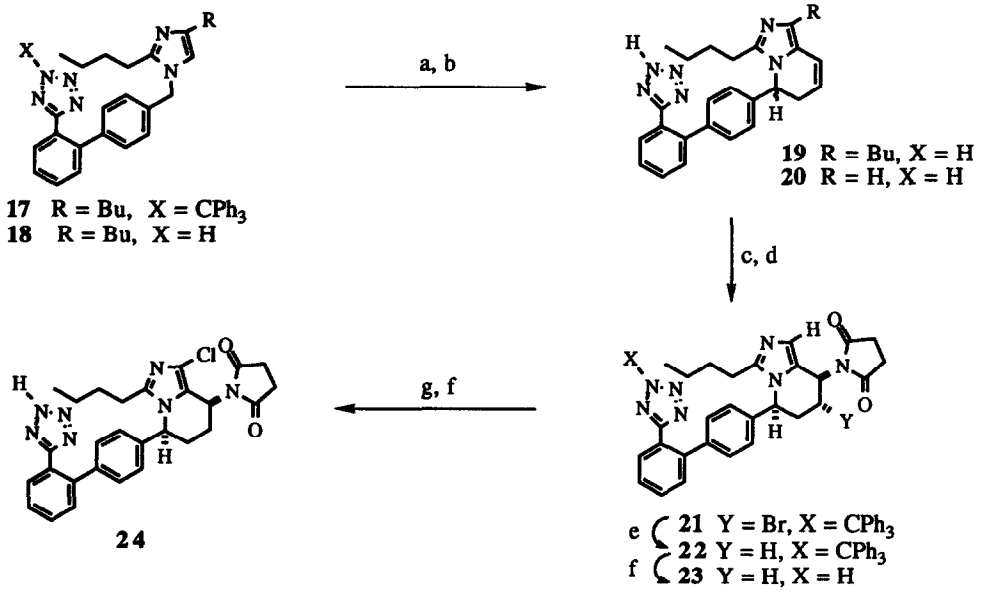
16

We next turned our attention to probe the second possibility. The conformationally restricted pyrazolone analogue **15**,[10] which does not have the ethyl linker to tie the biphenyl group to the heterocyclic sidechain, was prepared (IC_{50} = 45,000 nM). Compared with its flexible parent pyrazolinone **16** (IC_{50} =

500 nM),[10] this structural modification caused a 100-fold decrease in potency. The second possibility was therefore ruled out. From these results it was concluded that the active conformation of the AII antagonists at the receptor is different from that of the class 2 compounds. Our attention was then turned to investigate the alternative conformation in compound class 3.

The synthesis of analogues of compound 3 began with a trityl-protected imidazoyl biphenyl 17 as shown in Scheme II (free tetrazole 18 has an IC_{50} of 63 nM). The imidazole-based conformationally restricted AII antagonist 19 has an IC_{50} of 190 nM (or 95 nM assuming only one enantiomer was active) and a pA_2 value[11] of 6.3. When compared with the flexible parent compound 18, the structural modification to rigidify the conformation caused only a 50% decrease in the binding affinity, suggesting that the conformation of this compound is very close to the active conformation of the AII antagonists at the receptor. The 4-butyl group, which has been shown to improve binding affinity in several flexible AII antagonists,[6b-e] seems to have little effect in this conformationally restricted series. For example, compound 20 which lacks the 4-substituent was actually slightly more potent than 19 with an IC_{50} value of 120 nM. It was postulated that the steric interaction of butyl group at the 4-position with the linker ring may have pushed it into a less favorable orientation for good binding. Tetrazole 20 was protected with trityl chloride, and in the presence of excess succinimide, treated with NBS in acetonitrile to give bromosuccinimide 21.[12] The bromide was reduced with Bu_3SnH to succinimide 22 and was subsequently detritylated to give one of the most active

Scheme II[a]



17 R = Bu, X = CPh_3
18 R = Bu, X = H

19 R = Bu, X = H
20 R = H, X = H

21 Y = Br, X = CPh_3
22 Y = H, X = CPh_3
23 Y = H, X = H

24

[a] **Reagents:** (a) n- BuLi, $Br(CH_2)_2CH(OMe)_2$, DME; (b) NaOAc, HOAc, H_2O, reflux (two steps: 65%); (c) Ph_3CCl, Et_3N; (d) NBS, succinimide, CH_3CN; (e) n- Bu_3SnH, AIBN, C_6H_6, reflux; (f) 10% water in acetic acid; (g) NCS, CCl_4.

analogues as a racemic mixture, compound **23**, with an IC_{50} of 15 nM and a pA_2 value of 8.6.[12] As mentioned earlier, a flexible side chain at the 4-position may have unfavorably interacted with the linker ring. To reduce this unfavorable interaction, while still exploiting the beneficial effect of the 4-substituent in binding, a chloro analogue was prepared. Chlorination of imidazole **22** with NCS in CCl_4 and subsequent detritylation gave the most potent compound **24** with an IC_{50} of 11 nM (or 6 nM assuming that only one enantiomer is active), and a pA_2 value of 8.8.[12] Comparing succinimide **23** with unsubstituted analogue **20**, the introduction of a bulky succinimidyl moiety boosted the binding affinity by 10-fold. Although compound **20** has a double bond in the linker ring, which makes a direct comparison between the two analogues more complicated, it has been shown in a related series that analogues without the double bond actually were slightly less potent. We could therefore assume that the removal of a double bond does not contribute significantly to the enhancement of the binding affinity of succinimide **23**. Based on that assumption, one plausible explanation for this enhancement was that the succinimidyl group, as a hydrogen-bonding acceptor, has provided an additional favorable interaction with the receptor. Alternatively, the bulky *cis*- succinimidyl group may have shifted the conformational equilibrium to favor the active conformation with the biphenyl moiety in its axial position. A more extensive study to examine these hypotheses will be reported in the future.

In summary, our investigation has led to the discovery of a series of potent, conformationally restricted AII antagonists which are more potent than the corresponding flexible parent compound. This discovery has helped to elucidate the interaction between biphenyl-based AII antagonists and the receptor, and may contribute to an understanding of the mechanism of angiotensin II agonist action at the receptor. A detailed report of the structure-activity relationship study will be published in due course.

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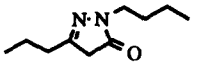
9. Inhibition of ^{125}I-labeled AII binding to the AT_1 receptor in rat uterine membranes. All compounds described in this article have IC_{50} (AT_2) values > 10 μM. Compounds were tested for binding to the AII receptor in rat uterine membrane preparations as described previously: Olins, G. M.; Corpus, V. M.; McMahon, E. G.; Palomo, M. A.; Schuh, J. R.; Blehm, D. J.; Huang, H.-C.; Reitz, D. B.; Manning, R. E.; Blaine, E. H. *J. Pharmacol. Exp. Ther.* **1992**, *261*, 1037-1043.

10. Compound **15** was prepared by heating pyrazolone **25** and a biphenyl aldehyde **26** in DMF using a modified procedure of Desimoni, G.; Gamba, A.; Righetti, P.P.; Tacconi, G. *Gazzetta Chimica Italiana*, **1972**, *102*, 491. Compound **16** was prepared by the alkylation of **25** with bromide **27**.



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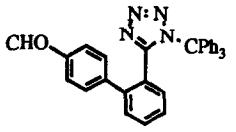

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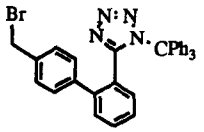

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11. Antagonism of AII-induced contraction of vascular smooth muscle. Compounds were tested for their ability to antagonize the AII-mediated contraction of rabbit aortic rings *in vitro* as described previously, see reference (9).

12. The relative stereochemistry assignment of these compounds were not rigoroursly established at this point. X-ray crystallographic sturcture determination is currently being pursued to confirm the stereochemical assignment. Results will be published in the near future.

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