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# Dibenzobicyclo[2.2.2.]octane Angiotensin II Receptor Antagonists.[1a]

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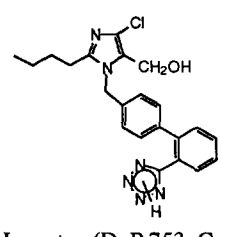
**Abstract**: Most angiotensin II antagonists in the literature contain the biphenyltetrazole moiety. We now wish to report a new, more rigidized biphenyl replacement, namely the dibenzobicyclo[2.2.2.]octane scaffold. It was designed on the basis of the three-dimensional conformation of the biphenyltetrazole moiety of losartan, the prototypic angiotensin II antagonist. This biphenyltetrazole replacement fixes both the imidazole and the negatively charged (at physiological pH) tetrazole in the same areas of space where they are located in losartan. Other scaffolds such as a fluorene and Rebek's Cleft are also discussed.

The angiotensin II (AII) antagonist losartan[1b] has currently finished Phase III clinical trials for the treatment of hypertension and has been approved in several countries in Europe. It acts by specific blockade of the angiotensin II subtype $1(AT_1)$ receptor which is responsible for the immediate pressor response induced by angiotensin II. Most subsequent AII receptor antagonists reported in the literature possess the biphenyltetrazole moiety attached to various heterocycles. However, some AII antagonists have incorporated changes in the biphenyl portion such as substituting one of the phenyl rings by a heterocycle[2-4] (figure 1), moving the acidic group to the linkage holding the two phenyl rings together[4, 5] (figure 2), or inserting a carbocyclic or heterocyclic spacer between the two phenyl rings[6, 7] (figure 3).




Losartan (DuP 753, Cozaar®)

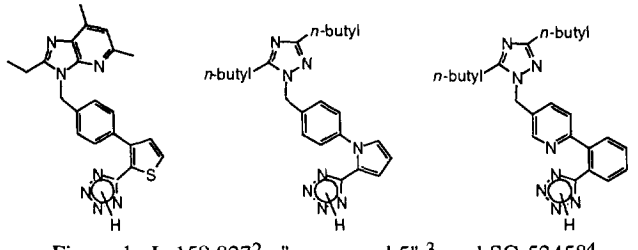



Figure 1: L-159,827[2], "compound 5" [3], and SC-52458[4].

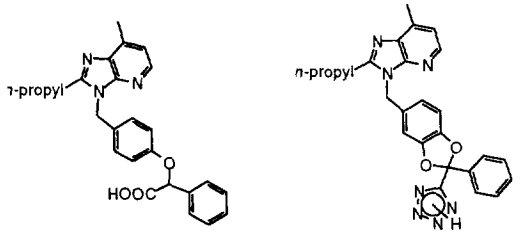
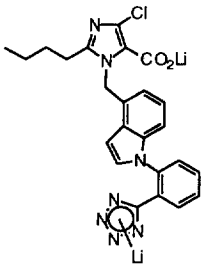
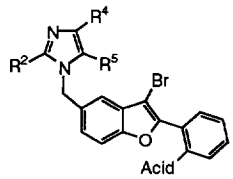



Figure 2. Phenoxyphenylacetic acid and benzodioxole biphenyl replacements.[4a,b]



BMS-180,560



| | Acid | $R^2$ | $R^4$ | $R^5$ |
|---|---|---|---|---|
| GR117289 | $CN_4H$ | *n*-butyl | Cl | COOH |
| GR138950 | $NHSO_2CF_3$ | ethyl | *c*-propyl | $CONH_2$ |

Figure 3. BMS-180,560 together with GR117289 and GR138950.

We decided to design a radically new biphenyl replacement based on the X-ray crystal structure of losartan. In this structure, the tetrazole lies over the plane of the phenyl ring attached to the -$CH_2$-imidazole (figure 4). We thought we could mimic this three-dimensional orientation of the acidic tetrazole group over a phenyl ring by employing the dibenzobicyclo[2.2.2.]octane, Rebek's Cleft[8], and the fluorene scaffolds.

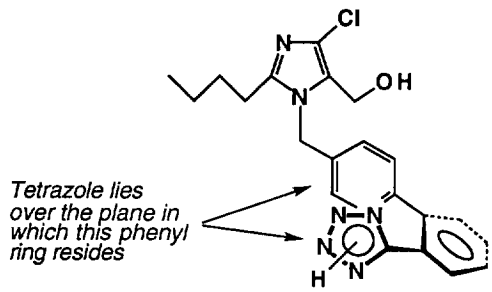



Figure 4. A representation of the three-dimensional orientation of losartan's biphenyltetrazole moiety in its X-ray crystal structure.

The dibenzobicyclo[2.2.2.]octane scaffold was easily synthesized via Diels-Alder reaction of anthracene derivative (1) with various dienophiles, such as maleic anhydride or dimethyl fumarate (figure 5). Our initial results with maleic anhydride led to an inseparable mixture consisting of compounds (2) and (3), together which exhibited mi= 1.1 μM) for the AII ($AT_1$) receptor.[9] We separated the dimethyl fumarate adducts via HPLC and found that both isomers (4) and (5) had essentially identical binding affi-nites which were three to five times greater ($IC_{50}$ = 0.2, 0.3 μM) than that observed for the mixture of (2) and (3).

The substitution of various acid isosteres for a carboxylic acid group played an important role in the discovery of losartan.[1b] The tetrazole seemed to work the best in that series and led to an increase of one order of magnitude in the binding affinity over that of the carboxylic acid. Applying what we had learned in the biphenyl series to the dibenzobicyclo[2.2.2.]octane series yielded tetrazole analog (9) (XD369) as a 9:1 ratio of isomers by NMR. As was the case in the biphenyl series, the binding affinity was now even greater for the tetrazoles ($IC_{50}$ = 0.09 μM). Intravenous administration of XD369 showed that it was more potent than losartan with an effective dose to lower the blood pressure by 30 mm Hg ($ED_{30}$) in the renal hypertensive rat (RHR) of 0.1 mg/kg (losartan $ED_{30}$ = 0.8 mg/kg).[10] Unfortunately, this compound was orally inactive.

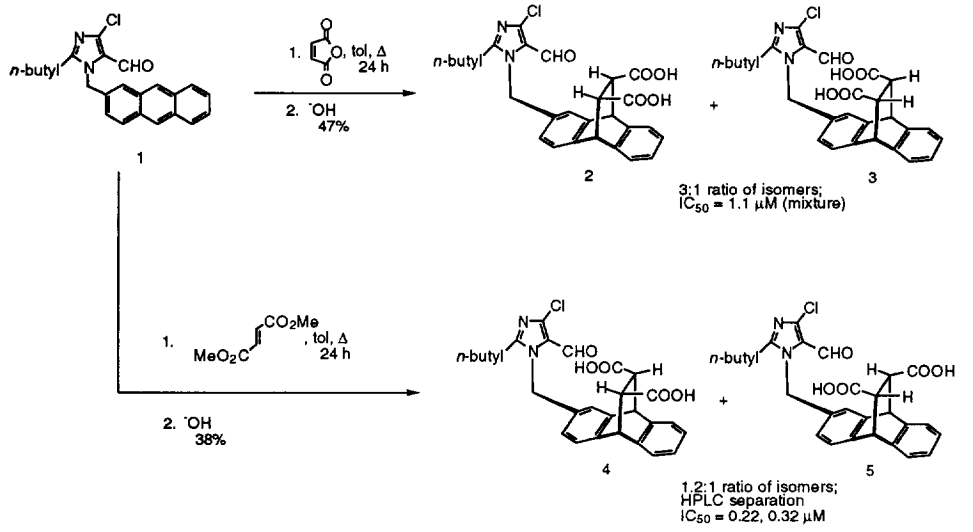



Figure 5. Synthesis of maleic anhydride and dimethylfumarate-anthracene adducts.

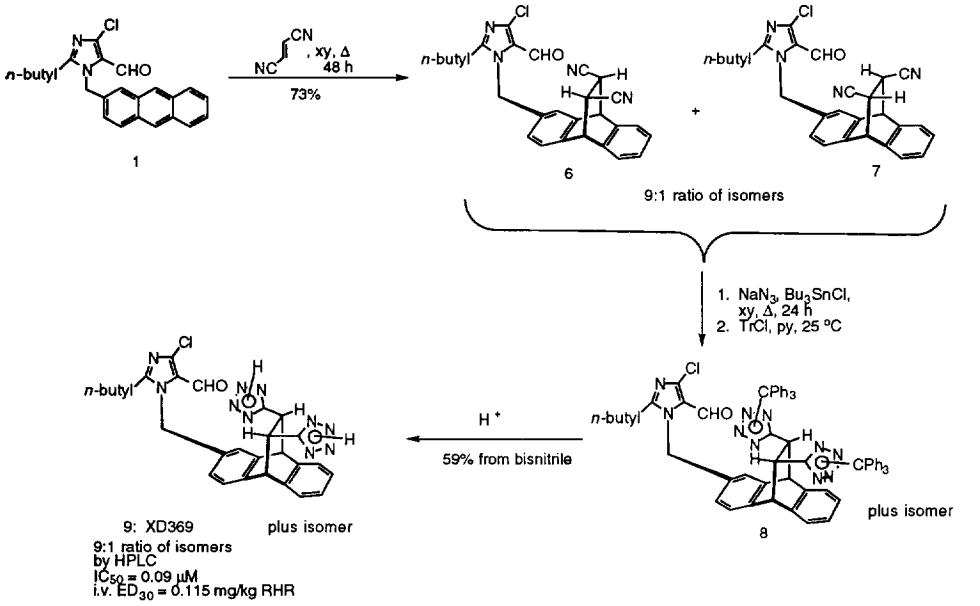



Figure 6. Synthesis of bistetrazole XD369 (9).

Intermediate (6) may undergo nucleophilic substitution reactions at the imidazole 4-position as shown in figure 7. Bistetrazole (11) (XD937) had a better blood pressure lowering profile than XD369 and this is shown in figure 8. The blood pressure was lowered to baseline (10 mg/kg cumulative i.v. dose) and could not be lowered any further by an additional intravenous dose of captopril (3 mg/kg i.v.).[10] XD937 had an $ED_{30} = 0.2$ mg/kg RHR, but it too did not lower blood pressure orally.

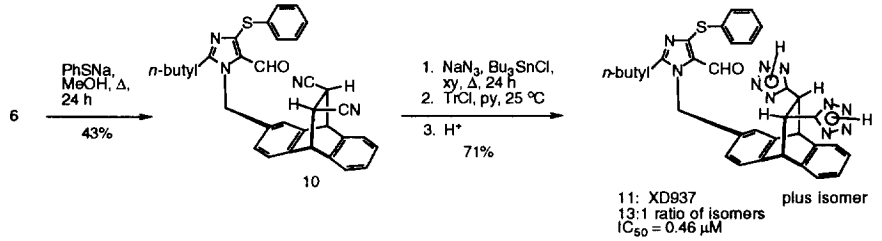



Figure 7. Synthesis of 4-phenylthioimidazole derivative XD937 (11).

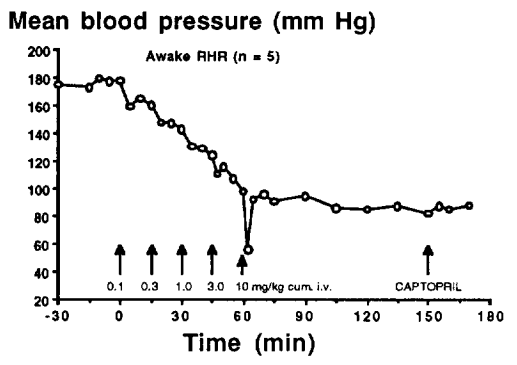



Figure 8. Blood pressure lowering curve for XD937 (11).

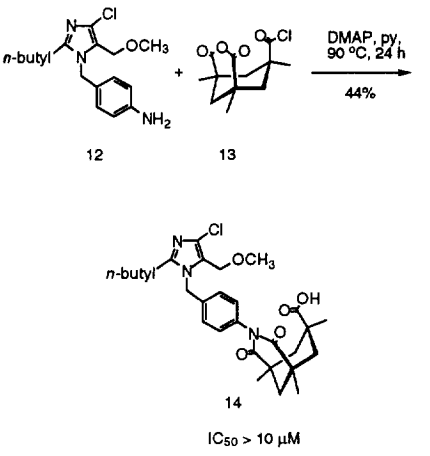



Figure 9. Synthesis of Rebek's Cleft derivative (14).

Synthesis of Rebek's Cleft-containing compound[8] (14) was carried out as shown in figure 9. It was hoped that the carboxylic acid would be rigidly held in the appropriate region of space in this analog as well. Unfortunately, the compound does not bind to the receptor, not because of the location of the carboxylic acid, but probably due to steric hindrance of the bulky imide portion. It has been shown previously[1b] that this part of the molecule can tolerate only an appropriately substituted aryl ring. The methoxymethyl side-chain has been shown before to be well-tolerated with respect to binding affinity.[11]

The syntheses of various fluorene template-containing compounds are shown in figure 10. Unfortunately, all of the compounds showed poor binding affinities. In the fluorene analog, the phenyl groups are restricted to be nearly coplanar. Replacement of the C-C single bond of the biphenyl portion of this fluorene skeleton with longer linkers, such as $-CH_2O-$ (a dibenz[b,e]oxepin ring system), has recently been shown to

lead to compounds with subnanomolar binding affinities.[12] We believe that this is due to greater conformational flexibility between the aryl rings, allowing them to assume a "biphenyl-like" non-coplanar conformation such as found in losartan.

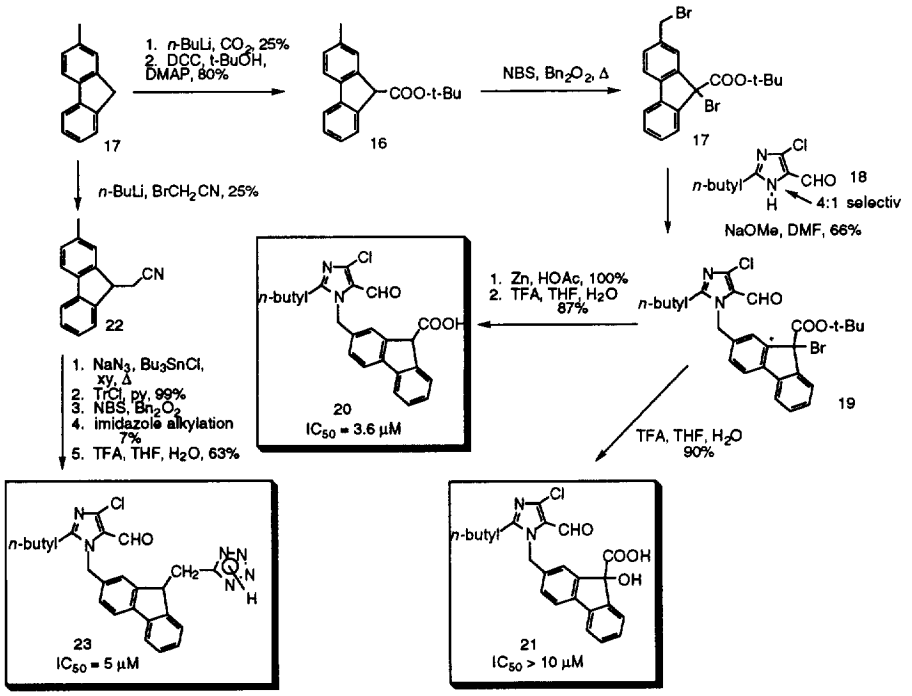
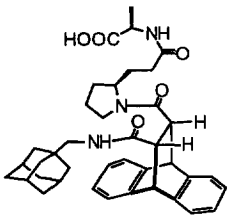



Figure 10. Synthesis of various fluorene-containing analogs.

**Conclusion.** Knowing where the functional groups of a flexible, biologically active molecule reside in space relative to one another, one may place them on a rigid template to come up with radically new structures that retain biological activity. The classic case in nature is that of enkephalin and morphine.[13]

We have shown that the rigid dibenzobicyclo[2.2.2]octane template permits the proper placement of all of the important functional groups of losartan in their correct three-dimensional orientation relative to one another: the imidazole, the aromatic ring, and the acidic group. The Rebek's Cleft and the fluorene skeletons did not yield compounds with high binding affinities in this case. However, they could potentially serve as templates for other classes of receptor antagonists.

The dibenzobicyclo[2.2.2]octane template is rather rare in medicinal chemistry. Very recently, it has been employed to make ligands such as (24) for the cholecystokinin (CCK) receptor.[14] The CCK receptor is a member of the seven trans-membrane spanning super family of G-protein coupled receptors as is also the AII receptor.[15] With that in mind, it might be possible to fine-tune the dibenzobicyclo[2.2.2]octane template so that one small change in the molecule will make it bind selectively to either the AII receptor or to the CCK receptor,



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mimicking the elegant work done by Hirschmann and coworkers with the glucose template.[16] Thus, as with the biphenyl template, which has yielded molecules having growth hormone secratogogue[17], neurotensin[18] and AII antagonist activity, the dibenzobicyclo[2.2.2]-octane series is also yielding molecules which bind to receptors which are part of the same superfamily.

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