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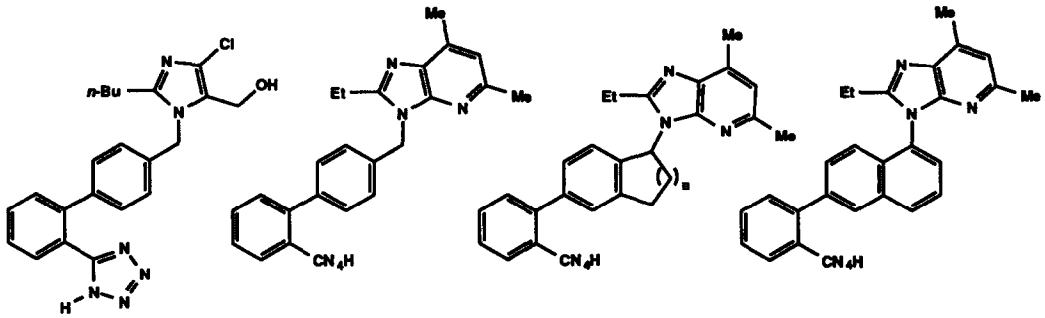
A CONFORMATIONALLY RESTRAINED SERIES OF AT_1-SELECTIVE ANGIOTENSIN II ANTAGONISTS

Philip A. Carpino,* Scott F. Sneddon#, Paul da Silva Jardine, George T. Magnus-Ayritey, Albert L. Rauch,// and Michael R. Burkard//

Department of Medicinal Chemistry, #Department of Computational Chemistry, //Department of Metabolic Diseases, Pfizer Central Research, Groton, CT 06340

Abstract: The benzyl linker in the angiotensin II receptor antagonist L-158,809 that separates the imidazo[4,5-b]pyridine ring and the 2-tetrazolylphenyl group was replaced by a series of bicyclic rings. The optimal bicyclic ring was found to be a dihydroindanyl group. Modification of the imidazo[4,5-b]pyridine group resulted in the discovery of a rigid analog that was as potent as L-158,809.

Losartan (formerly DuP 753) is the prototypical non-peptidic AT_1-selective angiotensin II (AII) antagonist and is currently undergoing advanced clinical study for the treatment of hypertension.[1] Since its discovery, there has been an intense effort to find other AII antagonists, one of the more interesting of which is L-158,809.[2,3] We investigated the possibility of locking the imidazo[4,5-b]pyridine ring and the 2-tetrazolylphenyl group in L-158,809 in a rigid conformation by tethering the benzyl linkage to the middle phenyl ring.[4] Specifically, this was explored using dihydroindanyl, tetrahydronaphthyl, tetrahydrobenzocycloheptenyl or naphthyl rings to separate the critical pharmacophores as depicted by compounds **1-4**. The results from this investigation demonstrate that such modifications can lead to potent conformationally restrained AII antagonists.



Losartan **L-158,809** **1** n = 1, **2** n = 2, **3** n = 3 **4**

The introduction of fused rings between the imidazo[4,5-b]pyridine and the 2-tetrazolylphenyl group eliminates the rotational flexibility of the benzyl group in the acyclic compound. The lowest energy

conformations of compounds **1-4** are shown in Figure 1 and are arranged so that the 2-tetrazoylylphenyl rings in the biphenyl systems coincide (not shown in figure).[5] The most noticeable difference between the minimized structures of **1-4** is the angle at which the headpiece projects from the plane of the middle phenyl ring.

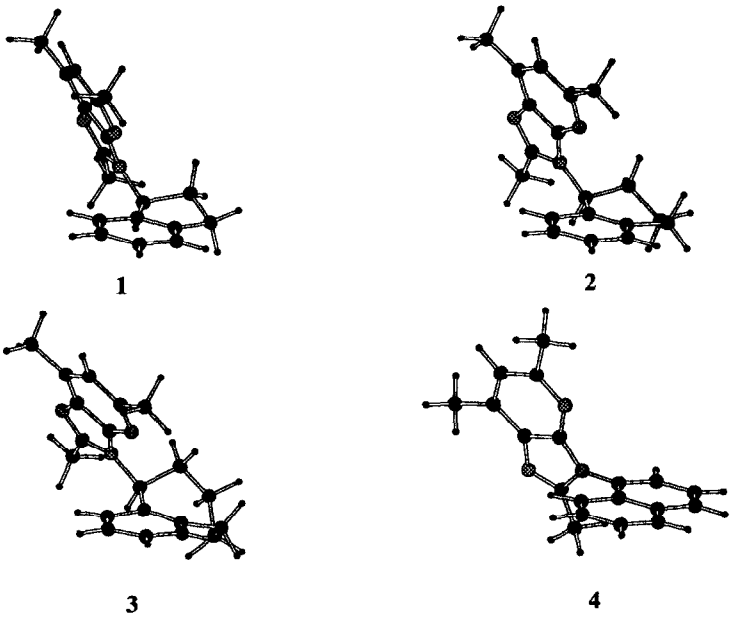


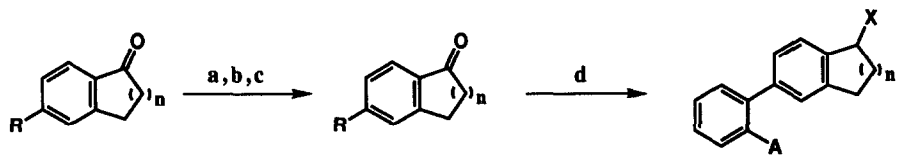
Figure 1. Minimized structures arranged so that the first ring of the biphenyl tetrazole moiety coincide (for clarity, the 2-ethyl substituent of the imidazopyridine is shown as methyl) .

Chemistry

The rigid analogs **1-3** were prepared as shown in Scheme 1.[6] Treatment of the phenols **5a**[7], **5b**[8] and **5c**[9] with triflic anhydride provided **6a-c** which were converted to the tributyltin derivatives **7a-c** with LiCl, hexabutylditin and $PdCl_2(PPh_3)_2$.[10] A Pd-catalyzed cross coupling of **7a-c** with 2-bromobenzonitrile provided the biaryl derivatives **8a-c**.[11] Reduction with sodium borohydride in methanol, followed by chlorination with $SOCl_2$ gave **10a-c**. Alkylation of these chlorides with the sodium salt of 2-ethyl-5,7-dimethylimidazo[4,5-b]pyridine provided **11a-c,** which upon treatment with trimethyltin azide in refluxing xylene afforded the desired antagonists **1-3**.[12] The analogs **15-19** were prepared in a similar manner using the appropriately substituted imidazo[4,5-b]pyridine.[13]

The naphthyl analog **4** was prepared by a different route (Scheme 2). The benzyl ether **12,** prepared from 1-amino-6-hydroxynaphthalene, was coupled with 2-chloro-3-nitro-4,6-dimethylpyridine[14] to give **13.** Reduction with H_2 and Pd/C followed by condensation with propionic anhydride yielded the imidazopyridine **14**. This was converted to **4** by: (i) treatment with triflic anhydride and pyridine; (ii) cross

Scheme 1



5a R = OH, n = 1
5b R = OH, n = 2
5c R = OH, n = 3

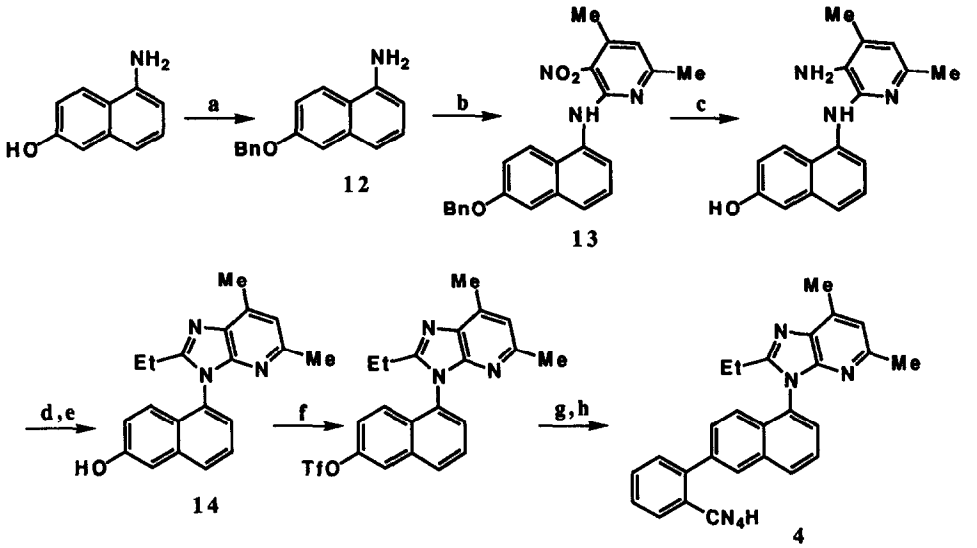
6a-c R = OTf
7a-c R = *n*-Bu_3Sn
8a-c R = 2-CNC_6H_4

e, f, g

9a-c A = CN; X = OH
10a-c A = CN; X = Cl
11a-c A = CN; X = NR_2
1-3 A = CN_4H; X = NR_2

Reagents: (a) Tf_2O,pyridine, CH_2Cl_2, 0 °C; (b) (*n*-$Bu_3Sn)_2$, $PdCl_2(PPh_3)_2$, DMF, 105 °C; (c) 2-BrC_6H_4CN, $PdCl_2(PPh_3)_2$, 1,4-dioxane, 105 °C; (d) $NaBH_4$, MeOH, 0 °C; (e) $SOCl_2$, pyridine, CH_2Cl_2, 0 °C; (f) imidazopyridine (HNR_2), NaH, 1,4-dioxane, 105 °C; (g) Me_3SnN_3, xylene, 145 °C

Scheme 2



Reagents: (a) $PhCH_2Br$, NaH, DMF, 23 °C; (b) 2-chloro-3-nitro-4,6-dimethylpyridine, NaH, KI, DMF, 130 °C; (c) Pd/C, H_2, EtOH, EtOAc; (d) $(EtCO)_2O$, 180 °C; (e) 2N NaOH, EtOH, 23 °C; (f) Tf_2O, pyridine, CH_2Cl_2, 0 °C; (g) 2-$(CN_4CPh_3)C_6H_4B(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, toluene, EtOH, H_2O, 85 °C; (h) MeOH, 50 °C

coupling the resulting triflate with the 2-trityltetrazolylboronic acid, $Pd(PPh_3)_4$ and K_2CO_3[15] and (iii) removal of the trityl group in refluxing methanol.

Discussion

The rigid analogs **1-4** all showed decreased binding affinity compared to the acyclic AII antagonist L-158,809 (IC_{50} = 0.2 nM). The IC_{50} values for **1**, **2** and **3** were 11, 120, and 220 nM respectively.[16] The binding affinity of this series decreased as the alkyl ring increased in size. The naphthyl analog **4** was equipotent to the indanyl analogue **1.**

The binding affinities of **1-3** suggest that none of the carbobicyclic templates places the pharmacophores in the optimized geometry for binding. The most potent compound in the series should be the one with the lowest energy penalty for rotating into the requisite binding conformation.

The conformation that each of these antagonists adopts upon binding to the receptor is not known. However, it may resemble one of the low energy conformers of the acyclic analog L-158,809. The minimized conformations of L-158,809 were determined by a molecular mechanics analysis of the two rotatable bonds (see $\chi 1$ and $\chi 2$, Figure 2) in the methylene bridge between the headpiece and the biphenyltetrazolyl tailpiece. Contour surfaces of the energy as a function of the $\chi 1$ and $\chi 2$ were constructed which showed a range of symmetrically disposed minima centered at $\chi 1 = 0°$, $\chi 2 = \pm 90°$ and $\chi 1 = \pm 120°$, $\chi 2 = \pm 60°$ (see blue/violet region of the contour map in Figure 2).

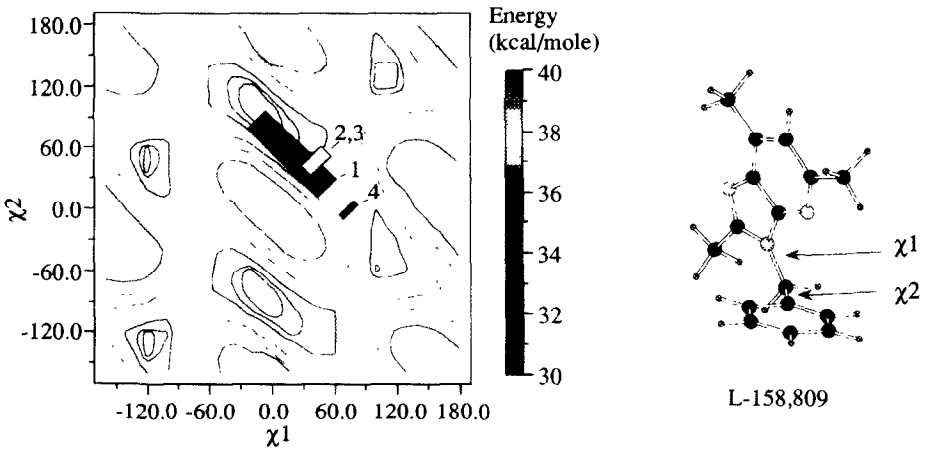


Figure 2. Energy contour map for rotation of the two bonds labeled $\chi 1$ and $\chi 2$ in L-158,809. The range of allowed $\chi 1$ and $\chi 2$ values for compounds **1**, **2**, **3** and **4** are shown in the blue, yellow and black rectangles labeled on the surface. Compound **1** has the greatest range of conformations and can attain a conformation similar to the low energy conformations of L-158,809

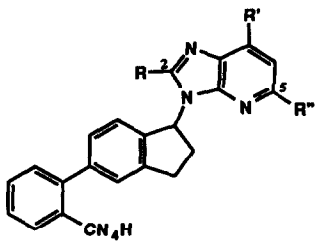
The minimized conformations of **1**, **2** and **3** were found to lie just outside the range of the minima for L-158,809 (Figure 2).[17] Energy calculations for **1** show that the indanyl ring can rotate 10 - 90° with an

energy cost of less than 1.0 kcal/mol, easily allowing the compound to adopt a conformation that lies somewhere in the range of the minimized (and possibly the binding) conformations of L-158,809. The small rotational energy penalty in **1** is due to the half envelope conformation of a five membered ring fused on one side to a phenyl group which makes many conformations all readily accessible. In **2**, the tetrahydronaphthyl ring exists in a pseudo-chair configuration in which the imidazo[4,5-b]pyridine headpiece is equatorial. A high rotational energy penalty (>1 kcal/mol) exists for moving the headpiece out of the equatorial position into a position that might better represent the optimized binding conformation. In **3**, the seven-membered ring also prefers an equatorial placement of the headpiece. Again, the energy penalty for rotating into potentially more favorable conformations is greater than 1 kcal/mol. This conformational analysis may explain the differences in binding affinities of compounds **1**, **2** and **3**.

The equal binding affinities of the naphthyl derivative **4** and the indanyl analog **1** are surprising. In **4**, the imidazo[4,5-b]pyridine headpiece is locked in an orientation orthogonal to the naphthyl ring. This rotational rigidity may be compensated for by a shift in the dihedral angle between 2-tetrazolylphenyl group and the naphthyl ring. A conformational analysis of this 2-tetrazolylphenyl naphthyl tailpiece shows that the energy cost is less than 0.5 kcal/mol for rotating the biphenyl system 0 - 30° from the perpendicular orientation. This may result in a more favorable alignment of the tetrazolyl group relative to the receptor. The binding affinity of **4** may be also explained by other factors such as a change in the electronic nature of the imidazo[4,5-b]pyridine headpiece due to conjugation with the naphthyl group, or to a specific liphophilic interaction between the bulky naphthyl ring and the receptor.

The dihydroindanyl analog **1** and the acyclic analog L-158,809 differ only in the linker group separating the pharmacophores. The decreased affinity of **1** as compared to L-158,809 may be due to unfavorable steric interactions of the substituents on the imidazo[4,5-b]pyridine headpiece with the receptor. For this reason, the substituent pattern on the headpiece was studied. The binding affinity of the series decreases if the C-5 methyl group is removed (see Table 1, **15**), if the length of the alkyl chain at C-2 is increased (**16**, **19**) or if the alkyl chain at C-2 is branched (**18**). These same trends were observed in the L-158,809 series. However, if the C-2 ethyl group is changed to a cyclopropyl group, binding affinity is restored to a level comparable to that of L-158,809 (**17**). The cyclopropyl group is smaller than an isopropyl group and now offers the best fit in this region of the receptor. The binding affinities of **1** and **17** show that the introduction of unfavorable conformational constraints in an acyclic compound may be offset by subtle changes elsewhere in the molecule in order to compensate for restricted rotational freedom.

Table 1



Compound	R	R'	R"	IC_{50} (nM)
1	Et	Me	Me	11
15	Et	Me	H	120
16	*n*-Pr	Me	Me	14
17	*c*-Pr	Me	Me	0.2
18	*i*-Pr	Me	Me	70
19	*n*-Bu	Me	Me	30
L-158,809				0.2

Conclusion

We have identified a new series of conformationally restrained AII antagonists. The replacement of the benzyl linker in L-158,809 with an dihydroindanyl group results in a decrease in binding affinity (**1**). A conformational analysis of this group shows that it has sufficient rotational flexibility to properly orient the pharmacophores in the receptor. By modifying the substituents on the imidazo[4,5-b]pyridine headpiece in **1**, a compound was found which had a binding affinity similar to the acyclic analog (**17**).

References and Notes

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6. Satisfactory 250 and 300 MHz ^{1}H NMR and mass spectral data were obtained for each analog prepared using chromatographically purified samples.
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16. The analogs **1-4** were assayed for the ability to displace ^{125}I-Sar^{1}Ile^8-AII from rat liver membranes in a preparation that was run without the presence of BSA. The results are reported as IC_{50} values which represent the concentration of the antagonist necessary to reduce radioligand binding by 50%. See: Chiu, A. T.; Duncia, J. V.; McCall, D. E.; Wong, P. C.; Price, W. A.; Thoolen, M. J.; Carini, D. J.; Johnson, A. L.; Timmermans, P. B. *J. Pharm. Exp. Ther.*, **1989**, *250*, 867-874.
17. The molecular modeling comparisons of L-158,809 and **1-3** all assume overlap of the 2-tetrazolylphenyl phenyl groups.

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