Bioorganic & Medicinal Chemistry Letters, Vol. 4, No. 1, pp. 41-44, 1994
Printed in Great Britain

0960-894X/94 $6.00 + .00

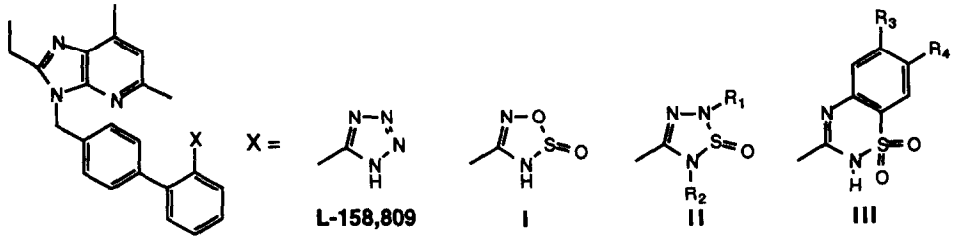
EVALUATION OF HETEROCYCLIC ACID EQUIVALENTS AS TETRAZOLE REPLACEMENTS IN IMIDAZOPYRIDINE-BASED NONPEPTIDE ANGIOTENSIN II RECEPTOR ANTAGONISTS

Dooseop Kim*, Nathan B. Mantlo, R. S. L. Chang†, S.D. Kivlighn†, and W.J. Greenlee

Department of Exploratory Chemistry, Merck Research Laboratories, P.O. Box 2000, Rahway, New Jersey 07065
†*Department of Pharmacology, Merck Research Laboratories, West Point, Pennsylvania 19486*

Abstract: A series of imidazo[4,5-*b*]pyridine-based AII antagonists incorporating heterocyclic acid equivalents, *e.g.*, oxathiadiazoles, thiatriazoles, and dioxobenzothiadiazines, are exemplified as novel non-peptide AII receptor antagonists. The most potent antagonist in this series, **L-161,177** (IC_{50} = 0.7 nM, rabbit aorta), bearing the oxathiadiazole, exhibited excellent *in vivo* profile after both iv and oral administration to conscious rats.

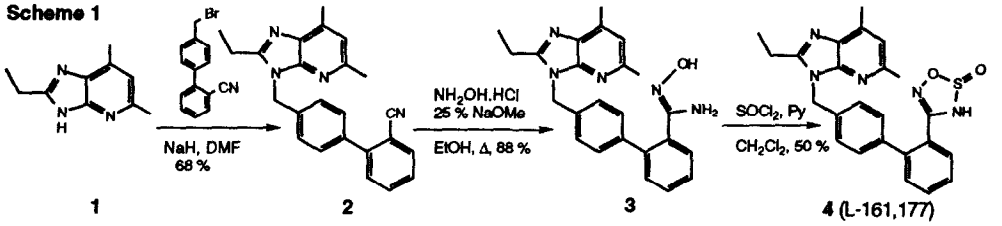
Introduction: The recent dramatic advances in the development of nonpeptide angiotensin II receptor antagonists can be attributed in good measure to the discovery of losartan (DuP 753),[1] which can trace its structural origin to the first nonpeptide AII antagonist series disclosed by Takeda.[2] Losartan has served as a prototype for numerous industrial AII antagonists programs. Since this discovery the strategy of replacing the imidazole of losartan with other heterocycles had brought about considerable success.[3] For example, our new class of imidazo[4,5-*b*]pyridine-based angiotensin II receptor antagonists, *e.g.*, L-158,809,[4] exhibited excellent *in vitro* and *in vivo* potency. Encouraged by the success of the imidazopyridine class we turned our attention to modification of the biphenyl-tetrazole moiety of L-158,809, common in most AII antagonists, for the exploration of novel AII antagonists series. Of particular interest was the replacement of the acidic tetrazole functionality by other acid equivalents.[5] Toward this end, various heterocyclic acid equivalents such as oxathiadiazole (I)[6], thiatriazole (II)[7], and dioxobenzothiadiazine (III)[8], were evaluated as tetrazole replacements. Herein we report the syntheses of potent AII antagonists incorporating the above acid equivalents, and their *in vitro* and *in vivo* profiles.



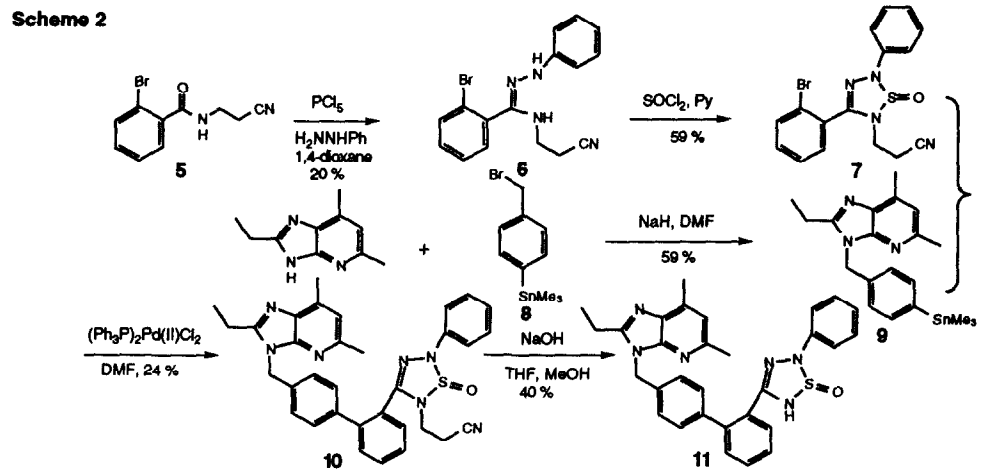
Chemistry: The synthesis of the imidazopyridine-based AII antagonists bearing the oxathiadiazole is outlined in Scheme 1. Imidazopyridine **1**[4] was treated with NaH and the biphenyl benzylic bromide[1] to give alkylation product **2**. The addition of hydroxylamine to nitrile **2** afforded amidoxime **3**, which was cyclized with thionyl

chloride to give oxathiadiazole **4** according to the literature procedure.[6] The synthesis of one representative example (**11**) of the three thiatriazole analogs in this study is depicted in Scheme 2.

Scheme 1

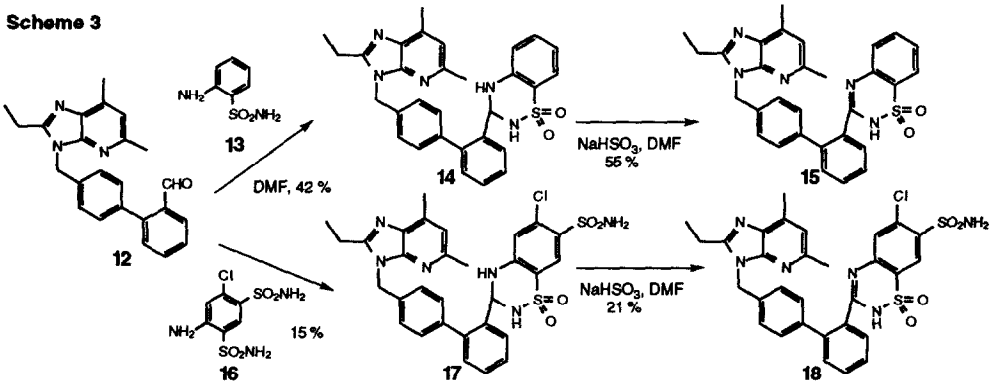


Scheme 2



Treatment of amide **5** with PCl_5 followed by the addition of phenylhydrazine to the resultant iminoyl chloride afforded amidrazone **6**.[9] The cyclization of **6** with thionyl chloride was followed by a Pd-catalyzed coupling of bromide **7** with aryltin **9** to give cyanoethyl-protected thiatriazole **10**, which was treated with aqueous NaOH to give thiatriazole **11**. Scheme 3 outlines the syntheses of both dihydro- and dehydro- dioxobenzothiadiazines.

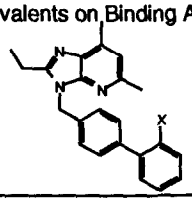
Scheme 3

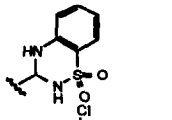
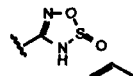
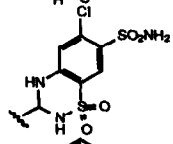
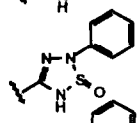
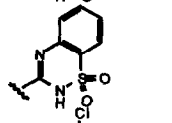
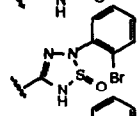
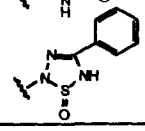
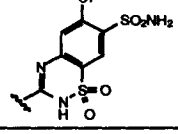


The condensation of aldehyde **12** with aminobenzenesulfonamides gave the dihydro- compounds **14** and **17**, which were treated with $NaHSO_3$ to afford dehydro- compounds, **15** and **18**, respectively.

Results and Discussion: The *in vitro* binding affinities of the compounds in Table 1 were determined by their ability to displace the specific binding ligand ^{125}I-Sar^1,Ile^8-AII from AT_1 receptors in rabbit aorta membrane preparations and are expressed as IC_{50} values.[10]

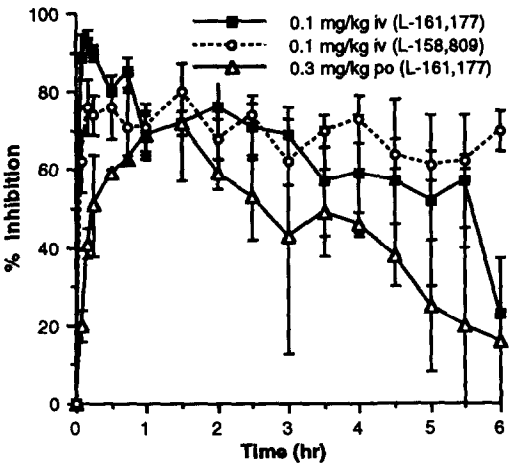
Table 1. Effect of Acid Equivalents on Binding Affinities of AII antagonists



compound	X	IC_{50} (nM)	estimated[11] pK_a of X	compound	X	IC_{50} (nM)	estimated pK_a of X
19	-CO_2H	3.8	5.1				
20		0.3	4.9	**14**		1300	>10.5
4		0.7	5.7	**17**		550	8.9
11		6	7.1	**15**		120	8.7
21		11	~7.1				
22		57	~7.1	**18**		6.5	7.0

All of the evaluated acid equivalents showed somewhat higher pK_a values in comparison to that of the tetrazole in L-158,809 (compound **20**, pK_a = 4.9). Oxathiadiazole **4** (L-161,177, pK_a = 5.7) is the most acidic outside of compounds **19** and **20**. It exhibited the best binding affinity to AT_1 among new antagonists in Table 1. Interestingly, compound **22**, in which the nitrogen is directly attached to the biphenyl is *ca.* ten fold less potent than its isomer **11**. Although chlorine or sulfonamide substituents may play an important role in receptor binding, the higher potency of dehydro- dioxobenzothiadiazines (**15** and **18**) than dihydro- ones (**14** and **17**) can be ascribed to the increased acidity of the dehydro- compounds. In the case of compound **18**, two electron withdrawing

Figure 1. Inhibition of AII Induced Pressor Responses in Conscious Rats by L-161,177 and L-158,809[12]



groups on the phenyl ring of dioxobenzothiadiazine resulted in both increased acidity and potency. *In vivo* potency of **L-161,177** was determined by assessing the inhibition of pressor responses to 0.1 μg/kg i.v. AII in conscious normotensive rats (Figure 1).[10] **L-161,177** produced a dose-related inhibition of the AII pressor response when administered intravenously. Compared to **L-158,809**, **L-161,177** showed slightly shorter duration.

In summary, we have demonstrated that three selected heterocycles, *i.e.*, oxathiadiazole, thiatriazole, and dioxobenzothiadiazine, can serve as new acid equivalents in AII antagonists design. The excellent *in vitro* and *in vivo* potency of **L-161,177** makes the oxathiadiazole an attractive acid equivalent for further exploitation in drug design.

Acknowledgment: We thank Dr. K. Owens and Ms. D. Levorse for the pK_a measurements, Ms. T.-B. Chen, K. Faust, and S. Scheck for the AII receptor assays, and Ms. G. Zingaro for the conscious rat assays.

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9. Duncia, J.V.; Pierce, M.E.; Santella III, J.B. *J. Org. Chem.* **1991**, *56*, 2395.

10. For the protocols for *in vitro* and in *vivo* assays, see reference 4.

11. The pK_a's (±0.2) of compounds **15** and **20**, and analogs of **4**, **11**, **14**, **17**, and **18** without imidazopyridine were determined in 1:1 MeOH/H_2O (v/v) at 22°C by potentiometric titration with standardized 0.1 M NaOH. The pK_a's of compounds **19**, **21** and **22** were estimated.

12. The data represent the mean % inhibition along with the standard error for n = 3.

(*Received* 2 *August* 1993; *accepted* 24 *September* 1993)