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SUBSTITUTED 1,3-BENZODIOXOLE & 1,3-BENZODITHIOLE -2-CARBOXYLATES AND THEIR TETRAZOLE ANALOGS WITH POTENT BINDING AFFINITY TO THE ANGIOTENSIN II AT_1 RECEPTOR

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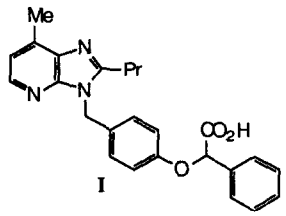
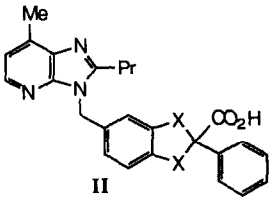
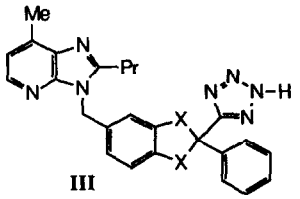
Abstract: Inspired by the modest success of a phenoxyphenylacetic acid (I) biphenyl tetrazole replacement, 1,3-benzodioxole-2-carboxylates and 1,3-benzodithiole-2-carboxylates (II) and their respective tetrazole analogs (III) were investigated as AII antagonists. These compounds, essentially conformationally restricted analogs of the phenoxyphenylacetic acid series, proved to be quite potent *in vitro*.



I



II



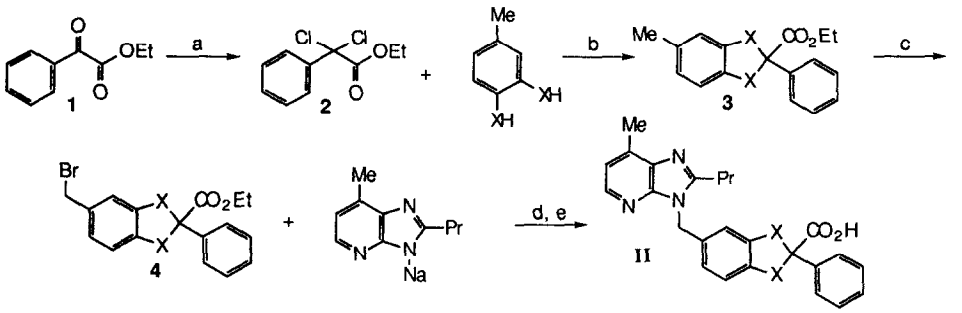
III

Introduction: Angiotensin II, the active hormone of the renin-angiotensin cascade, plays a critical role in the regulation of blood pressure and electrolyte balance. The remarkable success achieved by angiotensin converting enzyme inhibitors for the treatment of hypertension and congestive heart failure has generated considerable interest in the development of novel pharmacological agents designed to intervene in the renin-angiotensin system.[1] A common feature of many nonpeptide angiotensin II receptor antagonists in development is a biphenyl moiety bearing an acidic group on the ortho-position of the distal phenyl, typically a carboxylic acid or tetrazole. This biphenyl moiety is typically attached to a heterocyclic unit by a methylene or an oxymethyl linker.[2] A representative example of a potent AT_1 selective AII antagonist containing the heterocycle found in the three structures above along with the biphenyl tetrazole moiety has been described in the literature.[3] Recently it has been demonstrated that the biphenyl tetrazole could be replaced, albeit with a slight loss in binding affinity, by a phenoxyphenylacetic acid unit (I).[4] In an effort to improve on this design we prepared conformationally-restricted analogs of these compounds. 1,3-Benzodioxole-2-carboxylates and 1,3-benzodithiole-2-carboxylates (II) and their corresponding tetrazole analogs (III) were thus investigated.

Synthesis: The synthesis of the 1,3-benzodioxole-2-carboxylates and 1,3-benzodithiole-2-carboxylates (II) is illustrated in synthetic scheme I. Treatment of ethyl benzoylformate with PCl_5 in refluxing benzene for 16 hours afforded dichloro derivative 2 in quantitative yield. Reaction of 2 with neat 4-methylcatechol at 140-175°C for 20 minutes provided a modest 16% yield

of the ethyl 1,3-benzodioxole-2-carboxylate. The sulfur analog was prepared in good yield, by refluxing dichloride **2** in a solution containing 3,4-dimercaptoluene in isopropanol with 5 equivalents of K_2CO_3.[5] Not surprisingly, a small amount of isopropyl ester was also isolated from the reaction mixture. Benzylic bromination of **3**, with NBS and AIBN as catalyst in CCl_4, afforded a good yield of bromomethyl compound **4**. Alkylation of the sodium salt of the 7-methyl-2-propylimidazopyridine heterocycle[3] with the bromomethyl derivative **4** in DMF provided the desired ester precursor. Saponification of the ester with NaOH in MeOH provided the desired antagonists, **III**, as shown.[6]

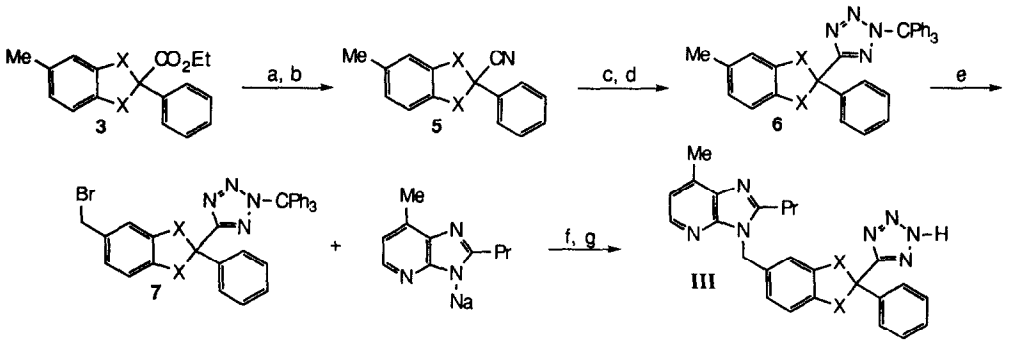
Scheme I



Reagents and Conditions

(a) PCl_5, PhH, reflux, 90%; (b) X = O: 140°-170°, neat, 20 min, 16%, X = S: reflux, i-PrOH, K_2CO_3,89%; (c) NBS, AIBN, CCl_4, 77-84%; (d) DMF, 25-35%; (e) NaOH, MeOH, 82-95%.

Scheme II



Reagents and Conditions

(a) NH_3, MeOH, 0°C, 100%; (b) $POCl_3$, NEt_3, 0°C to reflux, 81%; (c) Me_3SnN_3, refluxing toluene; (d) $ClCPh_3$, Et_3N, CH_2Cl_2, 86% for the two steps; (e) NBS, AIBN, refluxing CCl_4, 86%; (f) DMF, 30-40%; (g) HCl, MeOH, 80-90% yield.

The synthesis of the 1,3-benzodioxole-2-tetrazolates and 1,3-benzodithiole-2-tetrazolates (**III**) is illustrated in synthetic scheme II. Benzodithiole and benzodioxole ester **3**, from scheme I, was

efficiently converted to nitrile **5** in a two step sequence involving carboxamide formation with NH_3 in MeOH followed by dehydration with $POCl_3$. The trityl-protected tetrazole derivative (**6**), prepared from the nitrile by reaction with Me_3SnN_3 in refluxing toluene, followed by protection of the tetrazole with tritylchloride, was obtained in very good yield. Benzylic bromination with NBS and AIBN as catalyst afforded the desired bromomethyl derivative, **7**, in 86% yield. Alkylation of the sodium salt of the heterocycle with **7** in DMF, followed by trityl group deprotection with dilute HCl in MeOH, provided the desired product **III** in moderate yield for the two steps.

Results and Discussion: Evaluation of the benzodioxole carboxylate (**II**: X = O) and the benzodithiole carboxylate (**II**: X = S) analogs in a rabbit aorta binding assay[7] clearly demonstrated that there is little effect on potency resulting from restricting rotation around the phenoxyphenylacetic acid moiety.[8] In fact, the sulfur analog was essentially equipotent with phenoxyphenylacetic acid derivative **II**. The IC_{50} of the benzodioxole carboxylate and the benzodithiole carboxylate in the AT_1 receptor binding assay[7] was 56 nM and 34 nM, respectively. These compounds, much like the phenoxyphenylacetic acid, were devoid of any appreciable binding affinity to the AT_2 receptor. The IC_{50}'s for the benzodioxole carboxylate and benzodithiole carboxylate in our AT_2 (rat midbrain) binding assay[9] was 2.8 μM and 8.1 μM, respectively.

Unlike the biphenyl series of antagonists which experienced a substantial boost in binding affinity when the carboxylic acid was replaced by a tetrazole[2], the binding of the tetrazole analogs **III** was essentially equal to the acids. The IC_{50}'s in the AT_1 and AT_2 binding assays for the tetrazole analogs of the benzodioxole and the benzodithiole were 45 nM and 35 nM, and 16 μM and 15 μM, respectively.

Finally, this series of compounds has provided insight into the possible bioactive conformation of the phenoxyphenylacetic acid antagonists. The activity of these compounds suggests that a bioactive conformation of the phenoxyphenylacetic acids could very well mimic the constrained structure of the benzodioxoles and benzodithioles.[10] Because the conformation[11] of the phenoxyphenylacetic acids which mimic these compounds is a low energy conformation, a large increase in potency was not realized with the conformationally restricted compounds discussed in this paper.

Acknowledgment: We acknowledge Ms. Kristie Faust and Ms. T. B. Chen for the AT_1 and AT_2 angiotensin II receptor assays.

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3. AT_1 IC_{50} = 1 nM. Mantlo, N. B.; Chakravarty, P. K.; Ondeyka, D.; Siegl, P. K. S.; Chang, R. S. L.; Lotti, V. J.; Faust, A. K.; Chen, T. B. Schorn, T. W.; Sweet, C. S.; Emmert, S. E.; Patchett, A. A.; Greenlee, W. J. *J. Med. Chem* **1991**, 34, 2919.

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6. The structure assigned to each new compound is in accord with its mass spectrum (FAB) and high field NMR spectrum.
   Compound II (X = O): H^1 NMR (250 MHz, CD_3OD) δ 0.91 (t, 3H), 1.66 (m, 2H), 2.62 (s, 3H), 2.82 (t, 2H), 5.45 (s, 2H), 6.62 (dd, 1H), 6.69 (s, 1H), 6.79 (d, 1H), 7.13 (d, 1H), 7.31 (comp m, 3H), 7.65 (m, 2H), 8.18 (d, 1H).
   Compound II (X = S): H^1 NMR (250 MHz, CD_3OD) δ 0.85 (t, 3H), 1.62 (m, 2H), 2.60 (s, 3H), 2.70 (t, 2H), 5.41 (s, 2H), 6.71 (dd, 1H), 6.95 (s, 1H), 7.05-7.25 (comp m, 5H), 7.82 (m, 2H), 8.15 (d, 1H).
   Compound III (X = O): H_1 NMR (250 MHz, CD_3OD) δ 0.89 (t, 3H), 1.67 (m, 2H), 2.65 (s, 3H), 2.86 (t, 2H), 5.49 (s, 2H), 6.70 (dd, 1H), 6.81 (s, 1H), 6.88 (d, 1H), 7.16 (d, 1H), 7.41 (comp m, 3H), 7.58 (dd, 2H), 8.22 (d, 1H).
   Compound III (X = S): H^1 NMR (250 MHz, CD_3OD) δ 0.87 (t, 3H), 1.61 (m, 2H), 2.65 (s, 3H), 2.72 (t, 2H), 5.47 (s, 2H), 6.80 (dd, 1H), 7.08 (s, 1H), 7 11-7.25 (comp m, 5H), 7.55 (dd, 2H), 8.18 (d, 1H).

7. Rabbit aorta membranes were prepared as described in Chang, R. S.; Lotti, V. J.; Chen, T-B. *Biochem. Biophys Res. Commun.* **1988**, 151, 1213. For protocol details see reference 2(c).

8. The AT_1 IC_{50} of compound I is 43 nM.

9. Chang, R. S. L.; Siegl, P. K. S.; Clineschmidt, B. V.; Mantlo, N. B.; Chakravarty, P. K.; Greenlee, W J.; Patchett, A. A.; Lotti, V. J. *J Pharmacol Exp Ther.* **1992**, 262 (1), 133-138.

10. It is also possible that the 1,3-benzodioxoles and the 1,3-benzodithioles position the critical pharmacophoric elements for receptor binding in an improved orientation compared to the phenoxyphenylacetic acid; however, this increase in binding affinity could be offset by the deleterious introduction of an additional heteroatom.

11. Molecular modeling was carried out using software developed at Merck Research Labs: J. D. Andose, R. A. Blevins, E. M. Flunder, T. Halgren, S. K. Kearsley, S. Sallamack and J. Shpungin, "AMF - The Advanced Modeling Facility', version 1.12, 1991, Merck Research Laboratories, Rahway, NJ 07065. Energy minimizations were carried out in OPTIMOL.

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