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NEW POTENT ANGIOTENSIN II RECEPTOR ANTAGONISTS CONTAINING PHENYLTHIOPHENES AND PHENYLFURANS IN PLACE OF THE BIPHENYL MOIETY.

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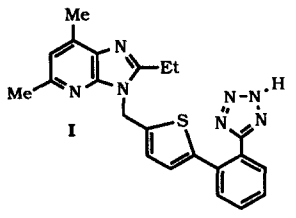
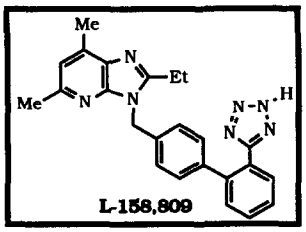
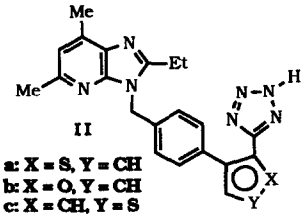
Abstract: The biphenyl fragment of the potent angiotensin II receptor antagonist L-158,809 was replaced by a phenylthiophene and a phenylfuran moiety. Replacement of the tetrazole-bearing phenyl by a thiophene resulted in a small loss in binding affinity (< 3X). Replacement of the central phenyl ring by a 2,5-disubstituted thiophene resulted in a thousand fold loss of potency.







Introduction:

Angiotensin II, an intermediate in the renin-angiotensin cascade, plays a critical role in the regulation of blood pressure and electrolyte balance.[1] 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.[2] During the past several years there have been extraordinary advances in the development of potent nonpeptide angiotensin II receptor antagonists.[3] A common feature of many of these antagonists is a biphenyl moiety bearing an acidic group on the ortho-position of the distal phenyl, typically a carboxylic acid or tetrazole. During the development of the potent angiotensin II antagonist L-158,809[4], we became intrigued by the importance of the biphenyl element in these antagonists. We decided to examine the effect of replacing either the central or distal phenyl ring of the biphenyl element by a thiophene or furan. Since we postulated that the function of the biphenyl fragment was to serve as a spacer element which places the acidic group in proper 3-dimensional orientation with respect to the remainder of the molecule, we anticipated that replacing either phenyl of the biphenyl element by a thiophene or furan might provide potent antagonists with distinct pharmacological profiles. Structures of type I and II were designed and compared to L-158,809 using molecular modeling.[5] It became apparent during the modeling of structure **IIa** that the important pharmacophoric elements appear to overlap those found in L-158,809 quite well (See Figure 2). On the other hand, replacement of the central phenyl by a thiophene or furan, as found in structure **I**, seems to have a more profound effect on the overall 3-dimensional orientation of the molecule (See Figure 1). When comparing the low energy conformations of structure **I** and L-158,809 the key tetrazole nitrogen containing the acidic proton, as well as the

distal phenyl, are displaced approximately 0.8 angstroms away from the position occupied by the corresponding nitrogen and carbons in L-158,809. While this may not appear to be a large distance, it may have a tremendous effect on receptor binding. In both structures I and II the rotational energy barrier about the phenyl-thiophene C-C bond is less than that of the biphenyl C-C bond.[5,6] This lowering of rotational energy may allow the structure to exist in conformations not optimal for receptor binding.

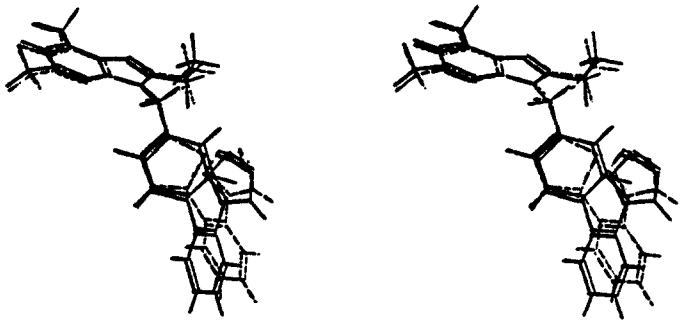


Figure 1. Inspection of the energy minimized conformations of I and L-158,809 by stereoscopic molecular graphics shows how, due to substitution of the thiophene for the central phenyl ring, the carbon and nitrogen atoms of the tetrazole moiety in structure I (structure represented as dashed lines) have been displaced by approximately 0.8 angstroms compared to the corresponding atoms in the parent structure L-158,809 (structure represented as solid lines). Alignment was achieved by fitting the three nitrogen atoms of the imidazopyridine and the methylene carbon between the imidazopyridine and the biaryl system.

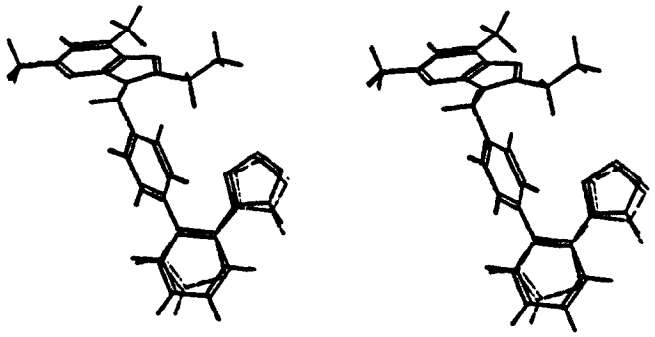


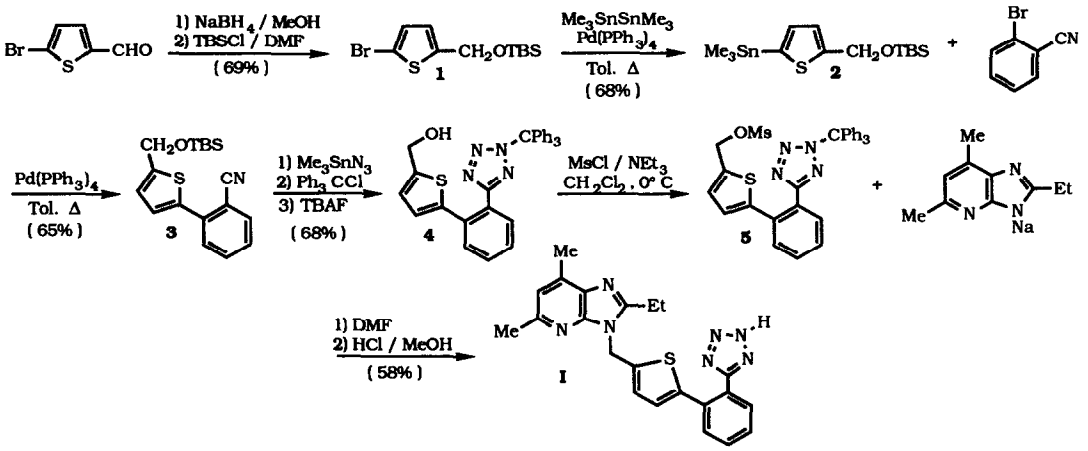
Figure 2. Inspection of the energy minimized conformations of **IIa** (structure represented as dashed lines) and L-158,809 (structure represented as solid lines) by stereoscopic molecular graphics shows a very close similarity in the conformations of both structures. Alignment was achieved by fitting the three nitrogen atoms of the imidazopyridine, all six carbons of the central phenyl ring and the methylene carbon between the imidazopyridine and the biaryl system.

Synthesis:

The synthetic route used to prepare structure I, the analog in which the central phenyl of the biphenyl element has been replaced by a thiophene ring, is outlined in scheme I. Reduction of 5-bromo-2-thiophene carboxaldehyde, with sodium borohydride in methanol, followed by

protection of the consequent alcohol as the t-butyl-dimethyl silyl ether provided bromothiophene **1** in 69% yield. Stannyl-halogen exchange was cleanly executed utilizing hexamethylditin in refluxing toluene with $Pd(PPh_3)_4$ as catalyst. Palladium catalyzed cross-coupling of the stannyl derivative with 2-bromobenzonitrile then affords phenylthiophene derivative **3** in 65% yield.[7,8] After the trityl protected tetrazole was constructed, the benzyl alcohol was unmasked with tetrabutylammonium fluoride. The mesylate, prepared with methanesulfonyl chloride and triethylamine in CH_2Cl_2, was reacted with the sodium salt of 5,7-dimethyl-2-ethylimidazopyridine[4] and the subsequent product deprotected to provide the desired potential antagonist in 69% yield for the two steps.[8]

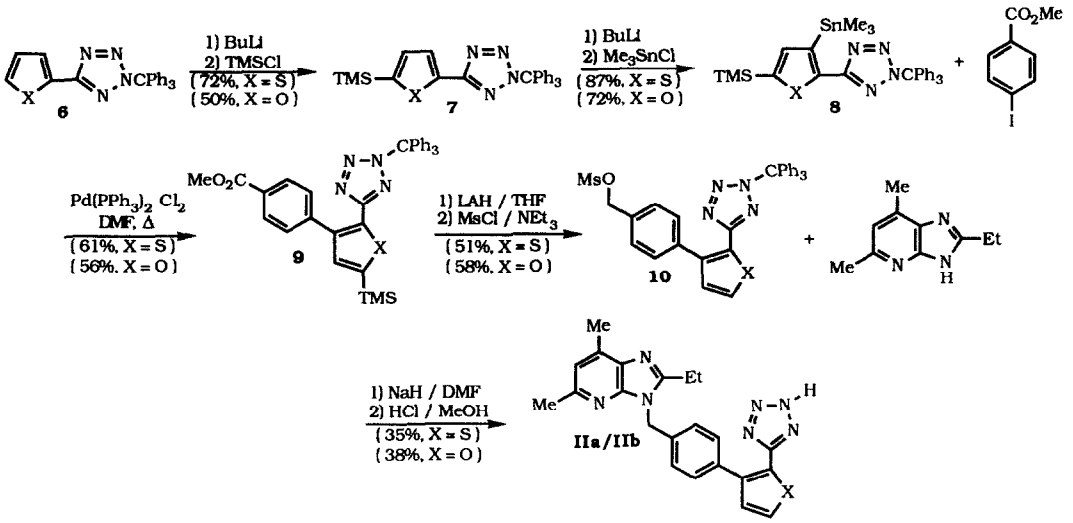
SCHEME I



The synthetic route used to prepare compounds of structure **IIa** or **IIb** (X = S or O and Y = CH), the analog in which the distal phenyl of the biphenyl element has been replaced by a thiophene or furan ring, is outlined in scheme II. The biaryl element was prepared using the palladium catalyzed cross coupling of an aryliodide with an arylstannane.[7] Initially we believed that we could position the trimethyltin in the 3-position of the heterocycle via a reaction of the dianion of compound **6** with trimethyltin chloride. Unfortunately due to the insolubility of the dianion as well as the capricious nature of the reaction, only very poor yields (< 20%) of the desired 3-trimethyltin derivatives were obtained. In an alternative procedure, selective deprotonation of the 5-position of the thiophene/furan with one equivalent of nBuLi, followed by protection with trimethylsilyl chloride, provided silyl derivative **7** in good yield. Metalation, now directed to the 3-position by the protected tetrazole, followed by reaction with trimethyltin chloride, afforded the desired 3-trimethyltin thiophene and furan derivative (**8**) in 87% and 72% yield, respectively. Palladium catalyzed cross-coupling with methyl 4-iodobenzoate afforded the desired phenylthiophene and phenylfuran derivatives in 61% and 56% yield, respectively. Reduction of the ester and concomitant removal of the trimethylsilyl[9] group with LAH was followed by reaction with methanesulfonyl chloride to afford the desired phenylthiophene and phenylfuran mesylates in 51% and 58% yield, respectively. Alkylation of the 5,7-dimethyl-2-

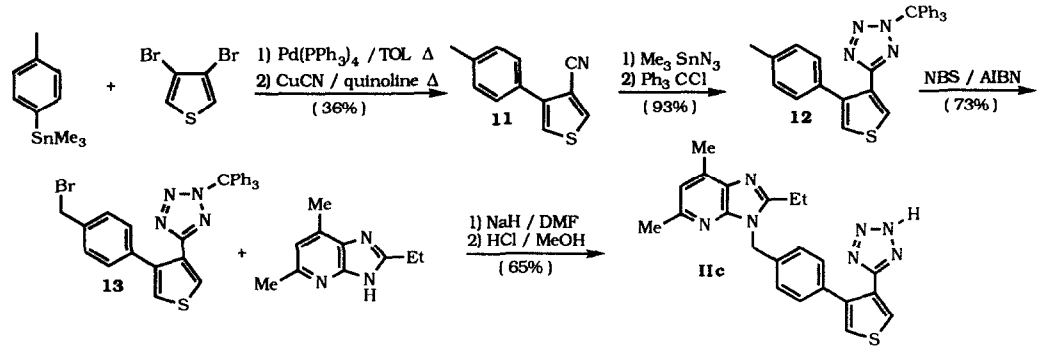
ethylimidazopyridine heterocycle, as depicted below, and trityl group deprotection of the subsequent product with HCl in MeOH completed the synthesis of the potential antagonists.[8]

SCHEME II



The synthetic route used to prepare **IIc** is outlined in scheme III. Here again a palladium catalyzed cross-coupling reaction was instrumental for the construction of the biaryl system.[7] Coupling of p-tolyltrimethyltin[10] with 3,4-dibromothiophene, followed by heating the crude product in quinoline with copper (I) cyanide, afforded the desired phenylthiophene derivative **11** in 36% yield for the two steps. Conversion of the nitrile to the protected tetrazole was cleanly accomplished using Me_3SnN_3 in refluxing toluene and trityl chloride with triethylamine to provide **12** in 93% yield. Benzylic bromination, using NBS with a catalytic amount of AIBN in refluxing CCl_4, provided the desired bromomethyl derivative **13** in 73% yield. Alkylation of the sodium salt of 5,7-dimethyl-2-ethylimidazopyridine in DMF with the newly prepared bromomethyl derivative was followed by removal of the trityl protecting group with HCl / MeOH to complete the synthesis of **IIc**.[8]

SCHEME III



Results & Discussion:

The IC_{50} of compound **I** in our angiotensin II rabbit aorta binding assay was 1 micromolar.[11] The substitution of thiophene for the central phenyl had resulted in a remarkable loss of binding of three orders of magnitude. This enormous loss in potency discouraged us from examining the 2,5-furanyl analog of compound **I**. However, as anticipated from our modeling studies, substitution of the distal phenyl with a thiophene (compound **IIa**) resulted in a much more potent antagonist. In this case only a three fold loss of AII receptor binding affinity was observed compared to L-158,809. Substitution of a furan for the thiophene (compound **IIb**) resulted in an additional 10 fold loss of binding affinity. The IC_{50}'s of **IIa** and **IIb** were 2.3 nM and 23 nM, respectively.[11] The 3,4-disubstituted thiophene isomer, compound **IIc**, had an IC_{50} of 2.4 nM in our angiotensin II binding assay. As expected, this was equivalent to compound **IIa**. Recognizing that the furan had a detrimental effect to the binding affinity of compound **IIb**, the furan analog of compound **IIc** was not prepared. Also, since the binding affinities of the 3,4-disubstituted thiophene and the 2,3-disubstituted thiophene (with the tetrazole in the 2-position) were equal, we believed there was no merit in pursuing the remaining thiophene isomer (2,3-disubstituted, where the tetrazole is in the 3-position).

In vivo evaluation of compound **IIa** (L-159,827) in our conscious rat assay at an i.v. dose of 1 mg/kg had a peak inhibition of angiotensin II induced increase in blood pressure of 90% with a duration of greater than 6 hours.[12,13] This activity is quite comparable to L-158,809 at that dose. Further *in-vivo* evaluation is pending.

In summary, we have demonstrated that the distal phenyl of the biphenyl element found in the potent angiotensin II antagonist L-158,809 can be replaced by a thiophene ring with only a slight loss of activity (~3X) or by a furan with a greater loss of potency (30X). Replacement of the central phenyl of the biphenyl by a thiophene resulted in a thousand-fold loss of potency compared to the parent structure, L-158,809.

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5. Molecular modeling was carried out using software developed at Merck Research Labs: J. D. Andose, R. A. Blevins, E. M. Fluder, T. Halgren, S. K. Kearsley, S. Sallamack and J. Shpungin, "AMF - The Advanced Modeling Facility", version1.12, January, 1991, Merck Research Laboratories, Rahway, NJ 07065. Energy minimizations were carried out in OPTIMOL.

6. A conformational search, executed by rotating 360° about the C-C bond of the biaryl, revealed that the energy of rotation of the aryl rings is decreased by 4 to 5 kcal/mol compared to the biphenyl. The difference in energy between the lowest energy conformation (a dihedral angle of 120°) and the highest energy conformation (a coplanar biaryl orientation, a dihedral angle of 0°) was 11.2 kcal/mol for L-158,809, 6 kcal/mol for **I** and 7.3 kcal/mol for **IIa**.

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8. The structure assigned to each new compound is in accord with its mass spectrum (FAB) and high field (400 MHz) NMR spectrum.

9. We intended to remove the trimethylsilyl group in a separate step, however, prolonged (24 hr) reaction with LAH at room temperatue cleanly afforded the des-silyl product.

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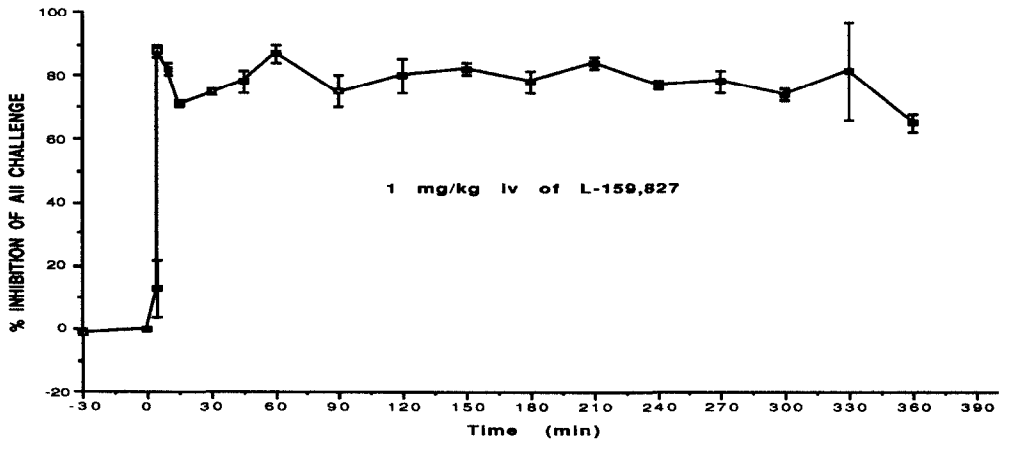
11. Rabbit aorta membranes were prepared as described in Chang, R. S.; Lotti, V. J.; Chen, T-B. *Biochem. Biophys. Res. Commun.* **1988**, 151, 1213. For protocol details see reference 4.

12.



13. For the protocol for testing in conscious rats see reference 4.