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SUBSTITUTED PHENYLTHIOPHENE BENZOYLSULFONAMIDES WITH POTENT BINDING AFFINITY TO ANGIOTENSIN II AT_1 AND AT_2 RECEPTORS

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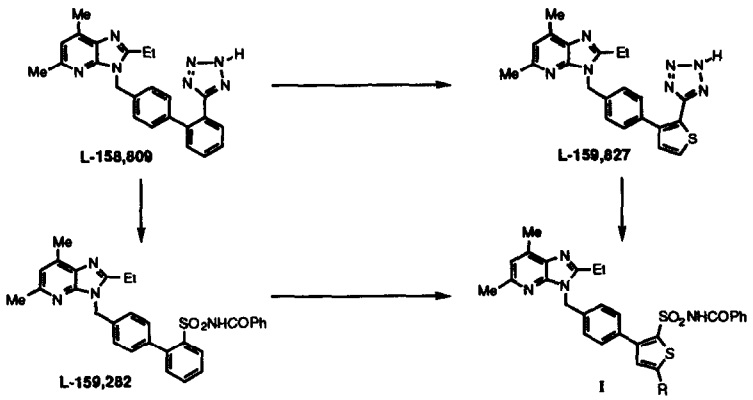
Abstract: Incorporation of a benzoylsulfonamide and a phenylthiophene group into the potent AII antagonist L-158,809 afforded compounds with a high affinity for the AT_1 receptor. Substitution at the 5'-position of the thiophene ring dramatically increased AT_2 binding affinity providing an analog with equal affinity for both AT_1 and AT_2 receptors.



Introduction:

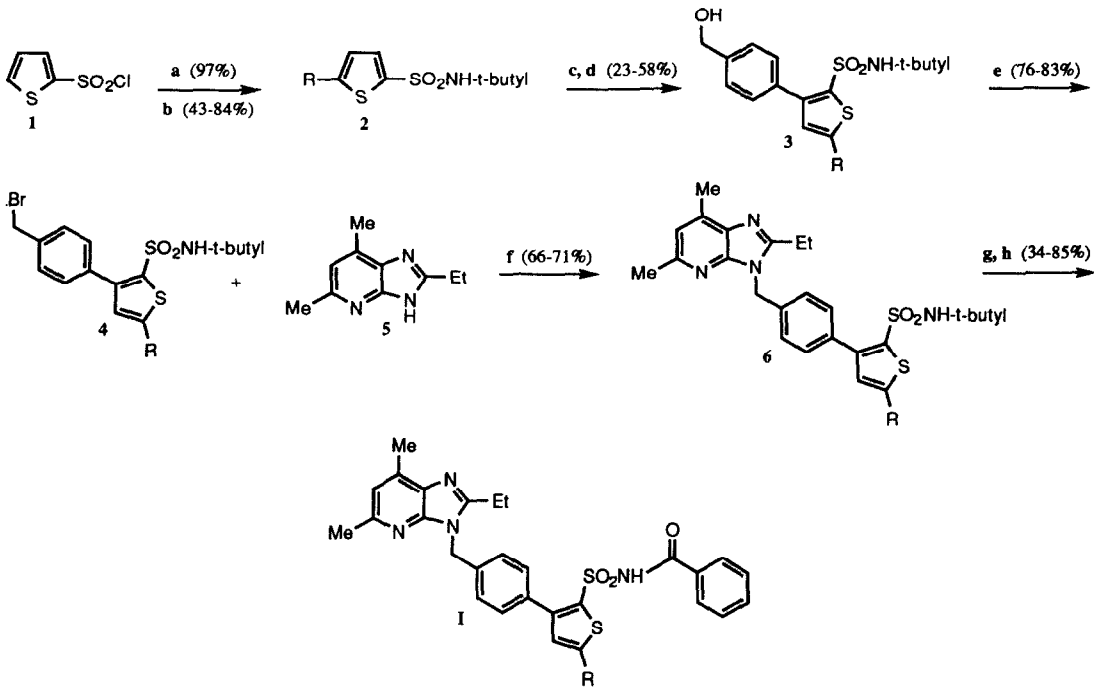
The renin-angiotensin cascade has a well established importance in the regulation of blood pressure and electrolyte balance.[1] Angiotensin converting enzyme (ACE) inhibitors block the conversion of angiotensin I (AI) to the potent vasoconstrictor angiotensin II (AII). ACE inhibitors have had great success in the treatment of hypertension and congestive heart failure,[2] and have generated interest in alternative ways to block the renin-angiotensin system. One important approach is the direct inhibition of AII binding to its receptors[3] of which there are two subtypes, AT_1 and AT_2. Inhibition of AII at the AT_1 receptor has been shown to be effective in the treatment of hypertension.[4] Many potent, nonpeptide AT_1-selective AII antagonists are currently being studied.[5] One such antagonist, losartan (DuP 753, MK-954),[4] is under Phase III clinical studies. While healthy volunteers treated with losartan showed reduced systolic blood pressure responses to AI, they also had increased plasma levels of circulating AII.[6] It is to be expected that these elevated levels of AII would have the potential to stimulate AT_2 receptors. Although the functional response to stimulation of the AT_2 receptor is not yet known, it was of interest to develop an antagonist which inhibits the binding of AII to both AT_1 and AT_2 receptor sites.[7]

Much of the recent work on non-peptide angiotensin II antagonists has focused on replacement of the substituted imidazole of losartan with other heterocycles. Maintaining the heterocycle as the substituted imidazopyridine of the potent antagonist L-158,809 (AT_1 IC_{50} = 0.8 nM; AT_2 IC_{50} = 37 μM),[8] we investigated the effects of modifications of the biphenyltetrazole moiety. The biphenyl element could be effectively replaced with a phenylthiophene as shown with the AT_1-selective antagonist L-159,827 (AT_1 IC_{50} = 2.3 nM; AT_2 IC_{50} > 30 μM).[9] Previous work from these laboratories has shown that the tetrazole of L-158,809 could be replaced with an acidic benzoylsulfonamide group providing the potent analog L-159,282 (AT_1 IC_{50} = 0.3 nM; AT_2 IC_{50} = 3 μM).[10] This compound also showed a modest increase in AT_2 binding potency. We expected that incorporation of both the benzoylsulfonamide group and thiophene 5-substituents into L-159,827 would lead to potent analogs with improved binding affinity at the AT_2 receptor.[11] In this paper we report the synthesis and *in vitro* evaluation of potent phenylthiophenes which block the binding of angiotensin II to both AT_1 and AT_2 receptors.

Synthesis:

The general procedure for synthesizing phenylthiophenes **Ia-Ih** (Table I) is shown in Scheme I.

SCHEME I



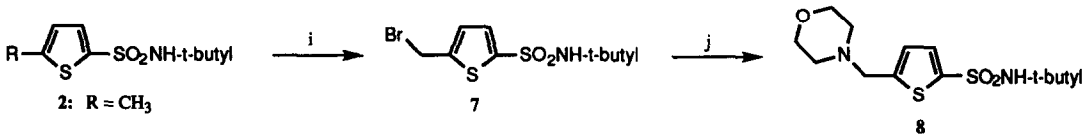
Reagents and Conditions

(a) t-BuNH$_2$, CH_2Cl_2. (b) 1) n-BuLi, THF; 2) RI. (c) 1) n-BuLi, THF; 2) triisopropylborate; 3) 2N HCl. (d) 4-bromobenzyl alcohol, NaOH or Na_2CO_3, toluene, EtOH, $Pd(PPh_3)_4$, Δ. (e) PBr_3, CCl_4. (f) NaH, DMF. (g) TFA, anisole. (h) benzoyl chloride, pyridine and DMAP or 4-pyrrolidinopyridine or benzoic acid, CDI, THF, DBU, Δ.

The t-butyl protected sulfonamide was prepared in excellent yield from 2-thiophenesulfonylchloride (**1**) on treatment with t-butylamine in CH_2Cl_2. The 5-position could then be selectively deprotonated with 2 equivalents of n-BuLi in THF. Treatment of the dianion with the appropriate alkyl halide provided the substituted thiophene **2** in generally good yields.[12] Treatment of **2** with 2 equivalents of n-BuLi again formed the dianion. This time the second anion resided at the 3-position as directed there by the sulfonamide. This anion was quenched with triisopropylborate and worked up with dilute acid to afford the boronic acid product. A palladium catalyzed cross-coupling of the crude boronic acid with p-bromobenzyl alcohol in a biphasic reaction under basic conditions afforded the biaryl product **3** in fair yields for two steps.[13] The benzyl alcohol was easily converted to benzyl bromide **4** upon treatment with PBr_3 in CCl_4. Coupling of bromide **4** to the substituted imidazopyridine **5**[8] with NaH in DMF was accomplished with good results. Deprotection of the t-butylsulfonamide **6** with TFA and anisole generated the free sulfonamide, which was acylated using one of two protocols. The first method was treatment of the free sulfonamide with benzoyl chloride and pyridine with either DMAP or 4-pyrrolidinopyridine as the catalyst. The second method involved treatment of benzoic acid with CDI in THF at 50°C, followed by reaction with the sulfonamide in the presence of DBU. Either procedure provided the final product, the benzoylsulfonamide **I**, in fair to excellent yield.[14,15]

The morpholinomethyl substituted product, example **Ii**, was prepared from 5-methylthiophenesulfonamide (**2**) (R = CH_3) as shown in Scheme II. The compound was treated with NBS and AIBN in CCl_4 to afford compound **7**. The bromomethyl derivative was then treated with excess morpholine to afford morpholinomethyl analog **8** in 77% yield. This derivative can be further elaborated to **Ii** as detailed in the general Scheme I.

SCHEME II



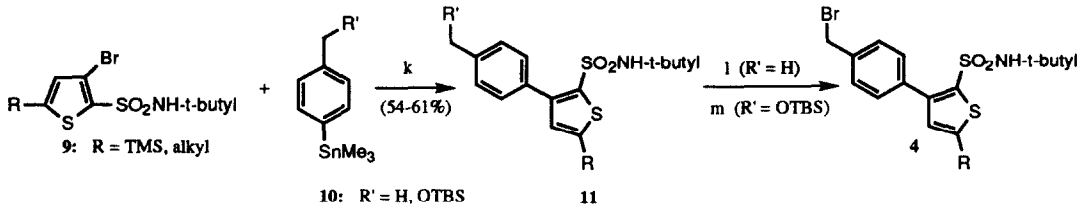
2: R = CH_3 7 8

Reagents and Conditions

i) NBS, AIBN, CCl_4, Δ. j) morpholine.

Other synthetic methods used included constructing the biaryl through the palladium catalyzed, trimethyltin coupling reaction shown in Scheme III.[16] Compound **Ia** was synthesized via this route by first protecting the reactive 5-position of the thiophenesulfonamide by treatment with n-BuLi and TMSCl according to Scheme I.[17] The dianion of **2** (R = TMS, alkyl) was formed as in Scheme I with 2 equivalents of n-BuLi and quenched with Br_2 to yield bromothiophene **9**. Bromide **9** was then coupled with p-tolyltrimethyltin or its hydroxymethyl analog protected with a t-butyldimethylsilyl group to form biaryl **11** in 54-61% yields. Treatment of **11** where R' = H and R = TMS with NBS and AIBN in CCl_4 afforded benzylbromide **4**. The silyl protecting group of compound **11** where R' = OTBS and R = alkyl was removed by treatment with HOAc, H_2O and THF to afford the benzyl alcohol. Conversion of the alcohol to the benzylbromide (**4**) on treatment with PBr_3 in CCl_4 was easily accomplished.[18] Compounds were then further elaborated to **I** as described in Scheme I.[19]

SCHEME III

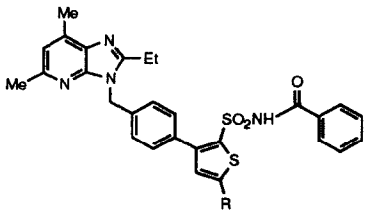


Reagents and Conditions

k) DMF, $Pd(PPh_3)_2Cl_2$, Δ. l) NBS, AIBN, CCl_4, Δ. m) 1) HOAc, H_2O, THF; 2) PBr_3, CCl_4.

TABLE I

***in vitro* AII Receptor Potencies**



Ex	R	IC_{50} (nM) AT_1	AT_2
Ia	H	1.5	25000
Ib	Methyl	0.3	4000
Ic	Ethyl	10.0	900
Id	Propyl	5.2	130
Ie	i-Butyl	24	22
If	Pentyl	7.5	150
Ig	Benzyl	10	150
Ih	TMS	44	190
Ii	Morpholinomethyl	87	120

Results and Discussion:

The IC_{50} of antagonist **Ia** (R = H) in the angiotensin II rabbit aorta binding assay[20] (AT_1) was 1.5 nM while the IC_{50} in the rat midbrain assay[21] (AT_2) was 25,000 nM. Compared to the phenylthiophenetetrazole L-159,827[9] (AT_1 = 2.3 nM and AT_2 > 30,000 nM) AT_1 and AT_2 activities were approximately the same. The most dramatic changes occurred on substitution at the 5-position of the thiophene ring as shown in Table I. AT_2 potency increased from 25,000 nM to 22 nM, a 1,000 fold gain in potency, shown in the case of example **Ie** (R = i-butyl). Although this compound exhibited a 16 fold loss in AT_1 potency relative to compound **Ia**, its excellent balance of binding affinities for the AT_1 and AT_2 receptors makes this compound particularly interesting as a lead for further modifications.

In order to examine the *in vivo* effect of the substitution of the benzoylsulfonamide for the tetrazole functionality, compound **Ia** was evaluated for its ability to block the pressor response to angiotensin II in conscious rats. At an i.v. dose of 1 mg/kg, peak inhibition of angiotensin II-induced pressor response was 93% with a duration of action which exceeded 4 h. Compound **Ia** has the same peak percent inhibition but a shorter duration than L-159,827 at that dose.[9]

Summary:

Beginning with AT_1 selective antagonists we have designed compounds with improved AT_2 potency including one (**Ie**) that binds equally well to both AT_1 and AT_2 receptor sites. We have demonstrated that an i-butyl substituent is optimal for balanced activity among those tested in the phenylthiophene series. We also showed that a benzoylsulfonamide moiety is an effective replacement for the tetrazole functionality in the phenylthiophene series. Compound **Ia** demonstrated an equivalent peak percent inhibition of angiotensin II induced increase in blood pressure *in vivo* with only a slight decrease in duration as compared to L-159,827. The functional activities of these compounds have yet to be determined. Efforts to obtain analogs with improved balanced activity and to increase their duration of action *in vivo* are underway.

Acknowledgment: We would like to thank Dr. Salah Kivlighn, Dr. Peter Siegl and Ms. Gloria Zingaro for their work with the conscious rat assays.

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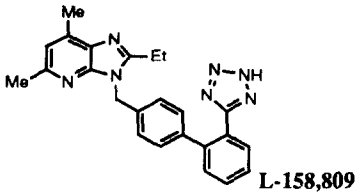
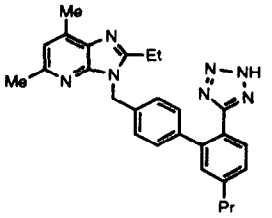
11. Propyl substitution at the 5'-position of the biphenyl increased AT_2 activity 18 fold as compared to L-158,809.



L-158,809



12. Compound **2** (R = Me) was obtained in lower yield (43%) due to alkylation at the 3-position as well as the 5-position. This 3-position alkylation was not observed in the other alkylations.

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14. A low yield of 34% for **Ig** (R = benzyl) was obtained. The method for acylation involved benzoic acid, CDI, DBU and THF. The low yield was due to problems removing the excess benzoic acid from the product.

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

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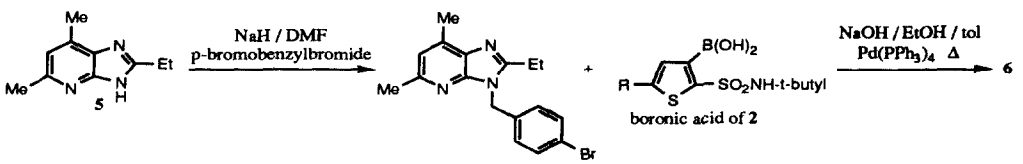
17. Compounds **Ia** and **Ih** were made concurrently. Partial removal of the trimethylsilyl group during deprotection of the sulfonamide with TFA and anisole afforded the precursor to **Ia**. The two compounds were separated by HPLC.

18. A Mitsunobu reaction could be used to couple the alcohol directly to the imidazopyridine in the presence of DIAD and triphenylphosphine in THF. This reaction, however, had limited utility as the product was difficult to purify from the reaction mixture.

19. Subsequently a more convergent route has been developed. Heterocycle **5** was coupled to p-bromobenzylbromide with NaH and DMF. This intermediate could then be directly coupled to boronic acid **2** to afford compound **6**. This shortens the synthetic pathway by two steps.



20. Rabbit aorta membranes were prepared as described in Chang, R. S. L.; Lotti, V. J.; Chen, T. B. *Biochem. Biophys. Res. Commun.* **1988**, *151*, 1213-1219. For the protocol details of testing in rabbit aorta membranes see reference 8.

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