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BALANCED AT_1 AND AT_2 ANGIOTENSIN II ANTAGONISTS. III. POTENT AND ORALLY ACTIVE 5- β-KETOSULFOXIDE IMIDAZOLYL BIPHENYL SULFONYLUREAS.

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Abstract:In the imidazolyl biphenyl sulfonylurea series, effects of substitution in position 5 of the imidazole ring with enolic ketone moiety were studied on AT_2 binding. β-ketosulfoxide, β-ketosulfone and β-ketoester proved to be highly effective substituents for potent nanomolar binding affinity on both AT_1 and AT_2 receptor subtypes. This led to the identification of β-ketophenylsulfoxide RU 64276 as a potent and orally active AT_1 antagonist and AT_2 binding inhibitor.

Angiotensin II (AII) is the potent endogenous vasoconstrictor agent of the Renin Angiotensin System[1] and its physiological responses are mediated through at least two distinct receptor subtypes,[2] designated as AT_1 and AT_2. The AT_1 receptor subtype is responsible for the pressor response and the majority of the known cardiovascular and renal effects[3] induced by AII. Losartan discovered by DuPont[4] and other AII antagonists[5] currently under clinical trials for treatment of hypertension are selective to this AT_1 receptor. A second AII receptor subtype, the AT_2 receptor, has been identified in various tissues using AT_2 selective ligands.[6] This receptor does not produce a pressor response after interaction with AII and at this time, no clear biological function can be attributed to the AT_2 receptor, even if some AT_2 mediated effects of AII have been proposed in various areas : cardiovascular and renal, central nervous system, growth and reproduction.[6,7]

In addition, in the clinic, healthy volunteers chronically treated with the AT_1 selective AII antagonist Losartan had increased plasma levels[8] of circulating AII and consequently AT_2 mediated effects as yet-unidentified could appear due to chronic overstimulation of the AT_2 site. Therefore, simultaneous inhibition of both receptors might prove advantageous and these reasons incited us, after the selection of our AT_1 selective imidazolyl biphenyl sulfonyl urea (HR 720)[9] for clinical development, to design balanced AII antagonists. Our objective was to discover orally active AII antagonists with subnanomolar or low nanomolar affinity for both AT_1 and AT_2 receptor subtypes. Contrary to AT_1 selective antagonists, little work has been published on balanced AT_1/AT_2 inhibitors apart from DuPont Merck and Merck in their imidazole, quinazolinone, triazolinone and imidazopyridine series.[10] In the imidazole series, DuPont Merck's investigators reported in particular the increase in AT_2 binding with introduction in position 5 of ester groups bearing large lipophilic substituents.[10a]

Our approach to balanced AII inhibitors of the AT_1 and AT_2 receptors was based on two previous discoveries we made : i) a benzyl side chain on the urea (compound **2**) dramatically increases AT_2 potency due to an interaction with a lipophilic pocket on the AT_2 receptor.[11a]

ii) an α-hydroxy acid moiety (compound **3**) in position 5 of the imidazole ring enhances AT_2 binding affinity.[11b] Both the hydroxy group, presumably due to H bonding with the AT_2 receptor, and the acidity of the carboxyl group were crucial for AT_2 potency.

Taking into account that the acetyl imidazole benzyl urea **4** exhibited an interesting AT_2 activity (IC_{50} = 30 nmol) with the carbonyl as a potential H-bond acceptor, we decided to see what would be the influence on the AT_1 and AT_2 binding affinities if we were to introduce an electron-withdrawing substituent onto the methyl in order to increase acidity of these protons (figure 1).

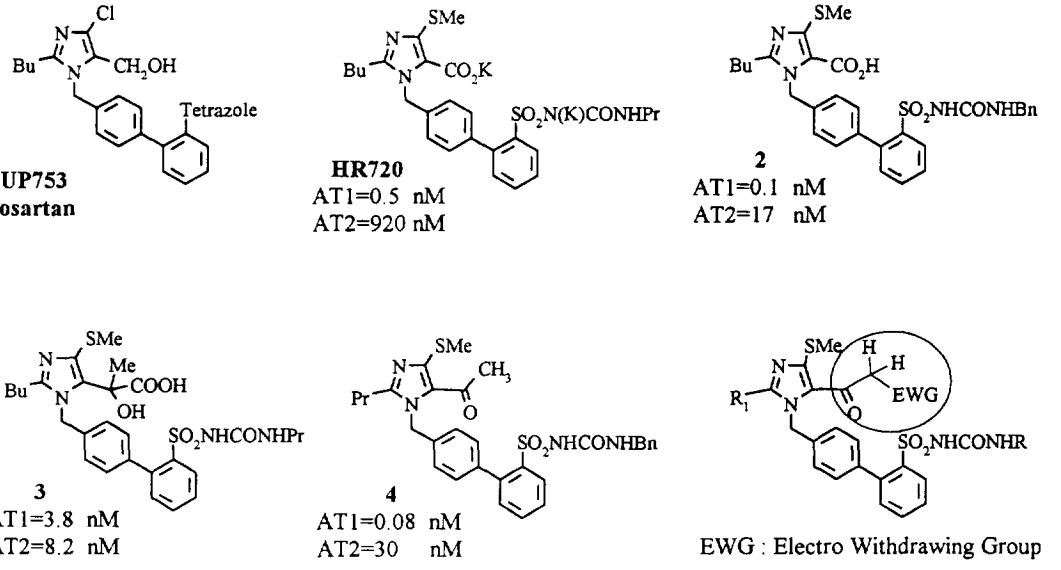
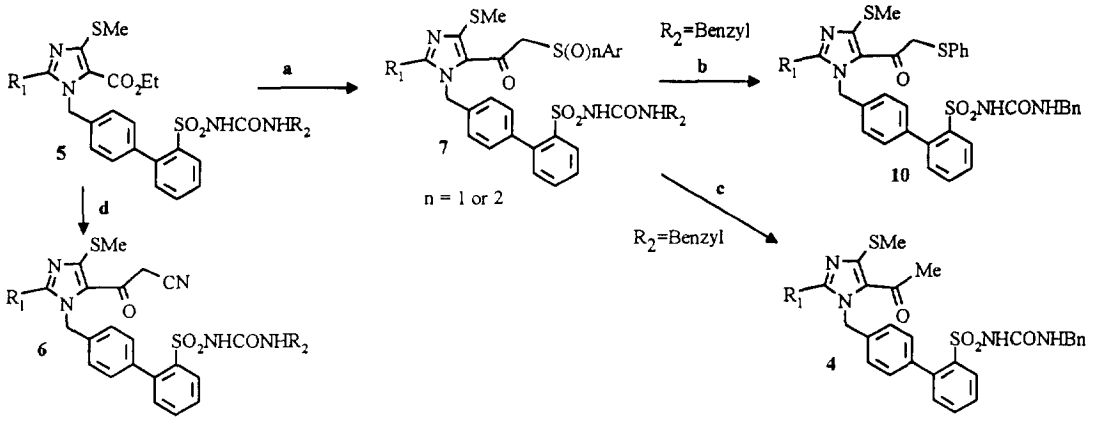


Figure 1

Synthesis

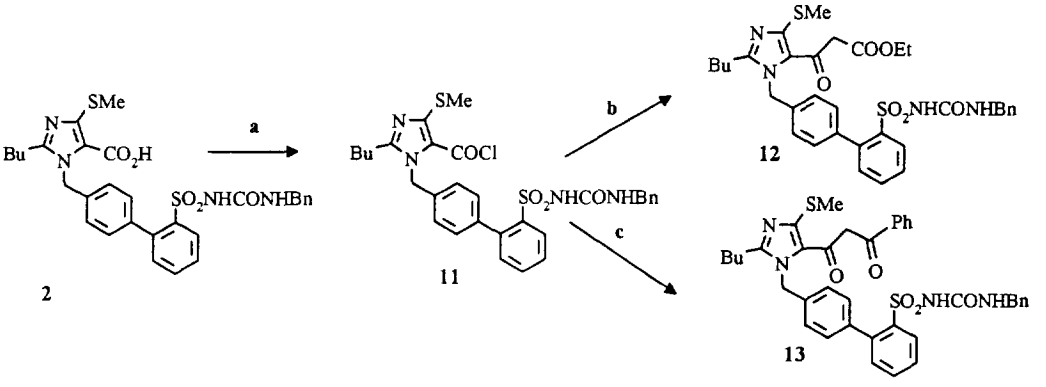
Synthesis of ester imidazole **5**, suitably substituted on the urea with a lipophilic side chain (benzyl, cyclohexylmethyl,...) has already been described.[9] Introduction of a β-ketosulfoxide (or sulfone) moiety (compound **7** and **8**) in position 5 of the imidazole ring was accomplished in good yield via reaction of the ester imidazole **5** with the anion of the requisite aryl methyl sulfoxide (resp. sulfone) generated *in situ* with LiHMDS at 0° C (Scheme 1). The same procedure was used for the preparation of β-ketonitrile **6** with anion of acetonitrile, in refluxing THF. β-ketosulfoxide **7** could be transformed to β-ketosulfide **10** by desoxygenation or to ketone **4** by desulfurization with Zn in an aqueous mixture of NH_4Cl/EtOH.

Scheme I



(a) LiHMDS (5eq), THF, $ArSO_2Me$, 65%-85% (b) NaI (3 eq), PTSA (3eq), CH_3CN, 15h, rt; (c) Zn, aq NH_4Cl/EtOH, rt, 15h; (d) LiHMDS, CH_3CN, THF.

Scheme II



(a) $SOCl_2$, toluene, 1h rt then 15h,55°C (b) EtOOC-CH_2-COOK, TEA, $MgCl_2$, AcOEt; (c) LiHMDS, THF, $PhCOCH_3$, -10°C, 10mn then **11**, -10°C to rt, 1h.

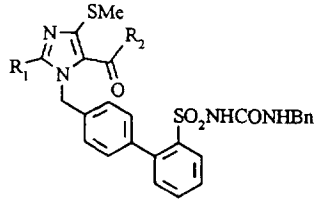
β-ketoester **12** and β-diketone **13** were prepared by treating the corresponding acid chloride **11** (generated from acid **2** with $SOCl_2$) with potassium ethyl malonate and the anion of acetophenone, respectively (scheme II).

Results and discussion

IC_{50} values of compounds listed in Tables 1 and 2 were determined by their ability to displace the specific binding of ^{125}I-AII from rat liver membranes (AT_1 receptors) and rabbit uterus membranes (AT_2 receptors).[9] Selected compounds were further evaluated *in vivo*, after intravenous or oral administration for their inhibition of the pressor response induced by A II (0.75 μg/kg i.v.) in normotensive pithed rats and are expressed as ID_{50} values.[9]

When compared with the acetyl group in position 5 of the imidazole ring (**4**, IC_{50} = 30 nmol) introduction of a β-ketosulfoxide **7b**, a β-ketosulfone **8b** or a β-ketoester **12** dramatically enhanced AT_2 potency with nmolar binding affinity (Table 1), suggesting that our initial hypothesis that increasing acidity of the methylene should improve AT_2 binding, was correct. However, things were not so clear with low AT_2 affinity of β-ketonitrile **6** (IC_{50} = 110 nmol). A possible explanation could be that previous sulfoxide, sulfone and ester groups were active essentially thanks to an H-bond interaction of the oxygen atom with the receptor which was impossible with the nitrile group. However, this would not explain the 40-fold decrease of β-diketone **13** compared to β-ketosulfoxide **7b** where both groups are able to make an H-bond interaction. The reasons for the discrepancy of the AT_2 activity, depending on the nature of the electrowithdrawing group, are still unclear. Moreover, substitution with a propyl chain on the methylene of β-ketosulfone (compound **9a**) decreased AT_2 binding affinity by two orders of magnitude when compared to **8b**.

Table 1



			IC_{50} [a] (nM)	
cpds	**R1**	**R2**	**AT1**	**AT2**
4	Pr	Me	0.08	30
7b	Bu	CH_2SOPh	0.04	3.0
8b	Bu	CH_2SO_2Ph	0.04	1.7
12	Bu	CH_2COOEt	0.09	1.0
6	Pr	CH_2CN	0.3	110
13	Bu	CH_2COPh	0.2	114
9a	Bu	$CH(nPr)SO_2Ph$	1.8	180

[a] See Table 2 for an explanation of tabulated data

Despite potent AT_1 binding affinity and consistently high antihypertensive activity after intravenous administration, β-ketoester **12** proved to be orally inactive at 3 mg/kg. Therefore, we decided to focus on the β-ketosulfoxide and β-ketosulfone series, and the role of the substitution (methyl, phenyl, substituted phenyl groups) on the sulfoxide (resp. sulfone) was evaluated (Table 2). In both series the phenyl group proved to be the most effective for AT_2 binding (**7b** *vs* **7a** and **8b** *vs* **8a**). Moreover, sulfone (**8a-b**) exhibited higher AT_2 potency than sulfoxide (**7a-b**). Conversely, the sulfoxides were orally active at lower doses than the corresponding sulfones and this incited us to work further on this sulfoxide series.

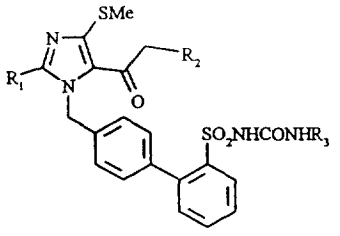
Taking into account that, in previous studies in the imidazole series, replacement of the butyl by a propyl side chain in position 2 of the imidazole ring slightly increased both AT_2 binding affinity and oral absorption, we synthesized **7c**, the 2-propyl analog of phenyl sulfoxide **7b**. **7c** exhibited a similar AT_2 binding with nanomolar

affinity for both AT_1 and AT_2 receptors but with a 2-fold improved oral activity (ID_{50} = 0.8 mg/kg). 2-ethyl imidazole **7i** was also prepared and showed comparable *in vivo* activity to 2-butyl imidazole **7b**, illustrating that in this series, propyl side chain in position 2 of the imidazole ring is the best substitution for oral activity.

We also studied the influence of chirality of the sulfoxide moiety and we found that the potency difference between the two enantiomerically pure p-tolyl sulfoxides **7g** and **7h** was marginal on both receptors.

Finally, we focused on the urea substitution (Table 2). A similar study on 5-carboxyl imidazolyl biphenyl sulfonyl ureas closely related to HR 720 had revealed the benzyl, cyclohexylmethyl, cyclopentylmethyl and CH_2-thienyl groups to be the most effective substitution of the urea for AT_2 binding.[11a] We thus synthesized urea analogs of phenyl sulfoxide benzylurea **7c**. These ureas **7d**, **7e** and **7f** showed high *in vitro* potency on both receptor subtypes but were found to be less active *in vivo* (po administration) than benzylurea **7c**.

Table 2



				IC_{50} [a] (nM)		ID_{50} [b] (mg/kg)	
cpds	**R1**	**R2**	**R3**	**AT1**	**AT2**	**iv**	**po**
7a	Bu	SOMe	Bn	0.30	15	0.06	0.7
7b	Bu	SOPh	Bn	0.04	3.0	0.12	1.6
8a	Bu	SO_2Me	Bn	0.08	5.8	0.04	1.7
8b	Bu	SO_2Ph	Bn	0.04	1.7	0.02	>3
8c	Bu	SO_2-pFluoroPh	Bn	0.06	0.8	0.12	>3
8d	Pr	SO_2-pMeOPh	Bn	0.10	2.1	0.07	2
10	Pr	SPh	Bn	0.20	93	NT	NT
8e	Pr	SO_2Ph	Bn	0.09	2.7	0.04	>3
7c	Pr	SOPh	Bn	0.08	2.8	0.04	0.8
7d	Pr	SOPh	CH_2*c*Hexyl	0.30	4.0	NT	3.1
7e	Pr	SOPh	CH_2-2-Thienyl	0.02	3.5	NT	1.4
7f	Pr	SOPh	CH_2*c*Pentyl	0.35	7.0	NT	>3
7g	Pr	SOpTolyl (+)	Bn	0.07	1.4	0.03	1.5
7h	Pr	SOpTolyl (-)	Bn	0.03	4.2	NT	1.5
7i	Et	SOPh	Bn	0.07	1.5	0.1	2.0

[a] IC_{50} for inhibition of specific binding of [^{125}I]AII to rat liver (AT1) and rabbit uterus (AT2) membrane preparation (n=2-4). [b] ED_{50} following intravenous (n=4) or oral (n=18-28) administration to pithed rats for inhibition of pressor response induced by infusion of AII. For details, see ref 9.

Conclusion

We have investigated a new series of imidazoles bearing a 5 β-ketosulfoxide (and sulfone) as balanced AII antagonists. As a representative member of this series, 2 propyl-4 thiomethyl 5 β-ketophenylsulfoxide imidazole linked to a biphenyl N-benzyl sulfonyl urea (compound **7c**, RU 64276) is a potent AII inhibitor that binds with nanomolar affinity to both AT_1 and AT_2 receptor subtypes. *In vivo*, this compound inhibited pressor response induced by AII (0.75 μγ/kg) in pithed rats, at low doses (0.04 mg/kg i.v. and 0.8 mg/kg p.o.). It may therefore be beneficial for the treatment of hypertension and may have advantages over HR 720 (our selective AT_1 antagonist) if AT_2 functions are proven to be physiologically significant.

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