Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 5, No. 22, pp. 2611-2616, 1995

0960-894X/95 $9.50+0.00

0960-894X(95)00479-3

BALANCED AT_1 AND AT_2 ANGIOTENSIN II ANTAGONISTS. II. POTENT 5 α-HYDROXYACID IMIDAZOLYL BIPHENYL SULFONYLUREAS

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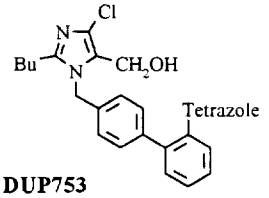
Abstract: Introduction of an α-hydroxyacid moiety in position 5 of the imidazole ring within the imidazolyl biphenyl sulfonyl urea series significantly increased AT_2 binding. Structure activity relationship around this moiety is described and gave rise to balanced AII inhibitors with nanomolar affinity on both AT_1 and AT_2 receptors and with an AT_2/AT_1 ratio of between 0.4 and 3.

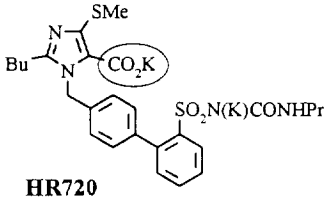
The discovery by DuPont of Losartan,[1] the first nonpeptide orally active angiotensin (AII) antagonist stimulated significant interest in blocking the Renin Angiotensin System at the receptor level and many other potent AII antagonists[2] are currently undergoing clinical trials for the treatment of hypertension and cardiac heart failure. They act by specific blockade of the AT_1 receptor subtype[3] which is responsible for the immediate pressor response brought about by AII. A second AII receptor subtype, designated as AT_2, has been identified in many tissues,[4] including human uterus, adrenal and brain. The function of this AT_2 receptor is much less clear even if some AT_2 mediated physiological effects have been proposed recently.[4,5]

Antagonism of the AT_1 receptor by Losartan has been found to significantly increase circulating AII levels[6] through blockade of feedback inhibition of renin release. These elevated AII levels could have the potential to stimulate AT_2 receptors and then could lead to yet-unidentified *in vivo* responses with possible deleterious effects. This incited us to develop new AII antagonists which inhibit the binding of AII to both AT_1 and AT_2 receptor subtypes.

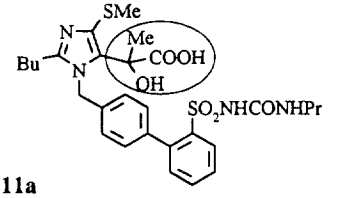
During further studies on the SAR of our imidazolyl biphenyl sulfonylurea HR 720 currently under clinical trials,[7] we discovered that an α-hydroxyacid moiety (compound **11a**) in place of the carboxyl group (HR720) in position 5 of the imidazole ring could dramatically enhance the AT_2 binding affinity of this



DUP753
Losartan



HR720
AT1=0.5 nM
AT2=920 nM



11a
AT1=3.8 nM
AT2=8.2 nM

antagonist with an AT_2/AT_1 ratio of 2 (IC_{50}=8.2 nmol on the AT_2 receptor). This interesting finding suggested a means of preparing more potent balanced AII antagonists.

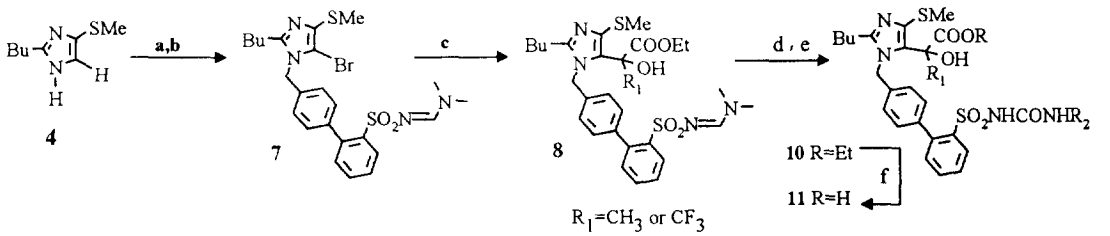
Recently, Merck and DuPont investigators reported nonpeptide AII antagonists[2a, 4, 5, 8] with high affinity for both AT_1 and AT_2 receptor subtypes and also studied the effects on the AT_2 binding of ester substitution[8a] at the imidazole 5-position. We describe herein the synthesis, SAR and pharmacological evaluation of a new series of imidazole biphenyl sulfonylureas substituted at the imidazole 5-position by an α–hydroxy-α–alkyl acid group. Compound **21e**, as a representative member of the series, showed balanced and subnanomolar binding affinity for both AT_1 and AT_2 receptors.

Synthesis

5 α–hydroxyacid imidazoles **11** and **21** have been synthesized according to different methods as depicted in Schemes I and II.

In Scheme I, the α–hydroxy ester group is introduced early in the synthesis via a halogen-metal exchange reaction. Starting from the substituted imidazole **4**,[9] a coupling step with bromomethyl biphenyl sulfonylamidine **5** afforded a 80:20 mixture of the N_1 and N_3 regioisomers which could be separated by flash chromatography. The desired N_1 isomer was then subjected to a bromination with NBS to give 5-bromoimidazole **7** in nearly quantitative yield. The key step of the synthesis is the formation of Grignard reagent obtained *via* halogen-metal exchange[10] between *i*PrMgBr and 5-bromo imidazole **7** and its *in situ* trapping with ethyl pyruvate or trifluoroethyl pyruvate in 48% and 96 % yield, respectively. The following steps have already been described[7] and can be summarized as follows : deprotection of the amidine in 1:1 refluxing mixture conc HCl/EtOH (84% yield), introduction of a propyl, benzyl or cyclohexylmethyl urea using the corresponding isocyanate in refluxing acetone in 80-94% yield (without addition onto the hydroxy group if no more than 1.1 eq of isocyanate is used) and final saponification to afford the α–hydroxyacid **11**.

Scheme I

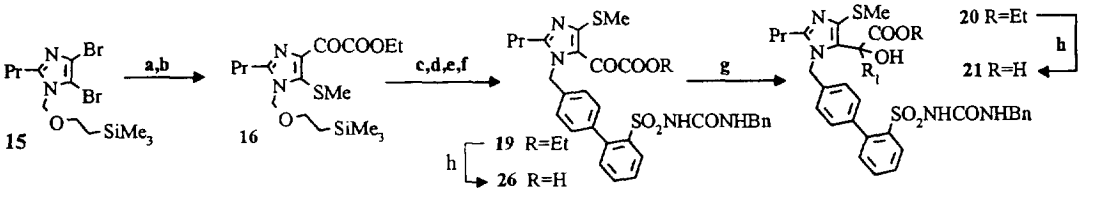


(a) $BrCH_2$-C_6H_4-C_6H_4-$SO_2NCHNMe_2$ (5), K_2CO_3, DMF, rt; 45h; 70% (b) NBS, CH_2Cl_2, 1h, rt, 98%;(c) *i*PrMgBr, THF, 30mn, r then $R_1COCOOEt$, 2h, rt.(d) conc HCl, EtOH, reflux 2 h; 84% (e) O=C=N–R_2(1.3eq), K_2CO_3(2 eq), acetone, reflux 1h (*f*) 2N NaOH, EtOH, rt, 24h.

In Scheme II, we adopted another strategy in order to introduce various alkyl substituents on the α-hydroxyacid moiety at the end of the synthesis. This could be performed by addition of the appropriate Grignard reagent on 5-α-keto ester imidazole **19** to afford α-alkyl-α-hydroxy ester **20**, which was then saponified to yield α-hydroxyacid **21**. The keto ester **19** was obtained from commercially available 2-propyl-imidazole, which was protected on nitrogen by a SEM group and dibrominated with NBS to give compound **15** in quantitative yield. Then, two regioselective and successive halogen-metal exchange/electrophilic addition sequences could be performed one pot or step by step (the latter gave a higher overall yield) : the sequence BuLi/MeSSMe functionalized position 5 of the imidazole ring in 77% yield and was followed by the reaction with BuLi/diethyloxalate (70 %) to afford the suitably substituted imidazole **16**.

After deprotection of the SEM group, the bromomethyl biphenyl sulfonylamidine **5** was condensed on free imidazole leading to the desired regioisomer in 68% yield. The amidine was then deprotected and the urea moiety was introduced using the same procedure as described in Scheme I to give ketoester **19**. Saponification of **19** also provided keto acid **26**.

Scheme II



(a) BuLi, THF, 15mn, -78°C then MeS-SMe, -78°C to rt, 1h, 77%. (b) BuLi, THF, 15mn, -78°C then EtOOCCOOEt, -78°C to rt, 1h, 70%.(c) TFA, CH_2Cl_2, refluxing, 15h, 92% (d) $BrCH_2$-C_6H_4-C_6H_4-$SO_2NCHNMe_2$ **5**, K_2CO_3, DMF, rt; 45h; 52% (e) conc HCl, EtOH, reflux 2 h; (f) O=C=N-Bn(1.3eq), K_2CO_3(2 eq), acetone, reflux 1h, 90% (g) RMgX (or $NaBH_4$), THF, 0°C to rt; (f) 2N NaOH, EtOH, rt.

Results and discussion

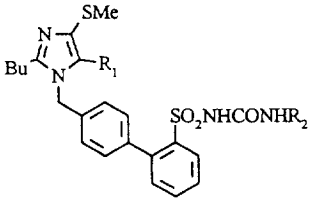
The *in vitro* binding affinity[7] listed in Tables I and II were determined by their ability to displace the specific binding of ^{125}I-AII from rat liver membranes (AT_1 receptors) and rabbit uterus membranes (AT_2 receptors) and are expressed as IC_{50} values.

As already mentioned, 5-α-methyl α-hydroxyacid imidazole **11a** exhibited surprisingly good AT_2 binding affinity when compared to the 5-carboxylic parent molecule HR 720 (8.2 nmol *vs* 920 nmol) indicating that position 5 of the imidazole ring could contribute significantly to AT_2 binding affinity. In addition, we had demonstrated previously[11] that suitable substitution on the urea side chain could also dramatically increase AT_2 activity and we identified benzyl and cyclohexylmethyl groups as the most effective side chains on the urea moiety. Combination of these two results led to compounds **11b** and **11c** (Table I) with expected increased AT_2 binding (albeit not as important as observed previously) when compared to propylurea **11a**.

Minor structural modifications on this α–hydroxyacid moiety have been investigated in order to better understand its role on AT_2 binding (Table I). The hydroxyl group proved to be essential for AT_2 potency since its removal (**25** *vs* **11b**) lowered AT_2 activity by three orders of magnitude, leading us to believe that the hydroxy group might be participating in a H-bond with the receptor. This result is correlated with the fact that ketoacid **26** imparted better AT_2 affinity (IC_{50} = 38 nmol), although not as potent as α-hydroxyacid **11b**. The acidity of this hydroxy group was also modified but without major change on affinity : replacing the α-methyl group by a α-trifluoromethyl group resulted in compounds **11d** and **11e**, which were slightly less active than **11c** and **11b**, respectively.

Esterification of the α-hydroxyacid group of **11a** resulted in the α-hydroxy ester **10a** with a more than 400 fold loss in AT_2 binding, while retaining potent AT_1 binding affinity (Table I). Moreover, β-hydroxyacid **30** also showed a 30-fold decrease in AT_2 potency when compared to **11b**. These data illustrate the crucial role and position of the acidic functionality for AT_2 binding, indicating a possible interaction with a putative basic site on the AT_2 receptor. The replacement of the carboxyl group (of α-hydroxyacid **11b**) by the isosteric tetrazole (**28**)[12] confirms the importance of the acid in that position, with similar binding between **11b** and **28** on both AT_1 and AT_2 receptor subtypes. As above, the keto tetrazole 27[12] was found to be 5 fold less active on AT_2 receptor than the hydroxy tetrazole **28**.

Table I : SAR of 5-α-hydroxyacid imidazole.

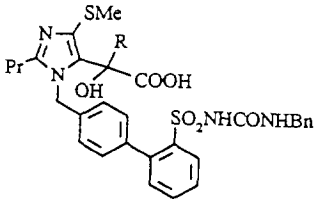


			IC_{50} [a] (nM)	
cpds	R1	R2	AT1	AT2
10a	C(OH)Me-COOEt	Pr	2.9	3500
11a	C(OH)Me-COOH	Pr	3.8	8.2
11b	C(OH)Me-COOH	Bn	0.5	3.9
11c	C(OH)Me-COOH	CH_2cHexyl	6.3	1.9
11d	C(OH) CF_3 -COOH	CH_2cHexyl	1.0	5.6
11e	C(OH) CF_3 -COOH	Bn	0.3	9.1
30	$CH(OH)CH_2$-COOH	Bn	0.2	120
25	CHMe-COOH	Bn	1.3	3800
26	COCOOH	Bn	0.2	38
27	COTetrazole	Bn	0.2	44
28	CH(OH)Tetrazole	Bn	0.5	8.0

[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).

A series of 2-propyl-5-α-alkyl α-hydroxyacid imidazoles was also synthesized in order to investigate the effects of substitution on the α-hydroxyacid moiety (Table II). It appeared that increasing the length of the substitution also increased AT_2 binding affinity (H **21a** 15nmol < Me **21b** 4.7 nmol < Et **21c** 2.0 nmol < iPr **21d** = Bu **21e** = hexyl **21f** = 1 nmol)). In fact, a large variety of substituents [alkyl C_2-C_6 , phenyl or benzyl] was acceptable. All these compounds **21c-h** showed low or sub nanomolar affinity on both AT_1 and AT_2 receptors as illustrated by **21e** (R = Bu :, IC_{50}= 0.5 nmol and 0.9 nmol). They displayed an AT_2/AT_1 ratio of between 0.4 and 3.

Table II



		IC_{50} [a] (nM)		ID_{50} [b] (mg/kg)	
cpds	R	AT1	AT2	i.v	p.o
21a	H	6.6.	15	NT	NT
21b	Me	3.9	4.7	NT	NT
21c	Et	2.5	2.0	0.25	>3 [c]
21d	iPr	2.8	1.1	0.49	NT
21e	Bu	0.5	0.9	0.46	4.9
21f	Hexyl	0.4	1.1	1.03	NT
21g	Ph	0.7	2.1	0.08	>3 [c]
21h	Bn	0.6	1.1	0.64	NT
21i	Vinyl	4.8	5.0	0.20	NT

[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] ID_{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.7. [c] <10% inhibition at 3 mg/kg.

These potent *in vitro* balanced antagonists have been evaluated *in vivo* after intravenous as well as oral administration for the inhibition of the pressor response induced by AII (0.75 μg/kg) in normotensive pithed rats.[7] Surprisingly, the intravenous potency of some of these compounds (**21f**, **21h**) is not consistent with their high AT_1 affinity, and substitution of the α-hydroxyacid moiety significantly modifies i.v. potency from 0.08 mg/kg (**21g**, R= Ph) to 1.03 mg/kg (**21f**, R= n-hexyl). Furthermore, none of these compounds displayed significant oral activity at 3 mg/kg in this model.

Conclusion

We have identified a new imidazole series of balanced AII antagonists which bind equally to both AT_1 and AT_2 receptors with subnanomolar (**21e**, RU 63455) or low nanomolar affinity. These compounds **21c-h** bearing an α-alkyl (or phenyl)-α-hydroxyacid in position 5 of imidazole and a benzyl sulfonylurea on the biphenyl fragment exhibited an AT_2/AT_1 ratio between 0.4 and 3. Unfortunately, they lacked potent *in vivo* efficacy especially after oral administration. However, they could be used as valuable tools for *in vitro* studies (**21e**) [and intravenous studies for **21g**] of balanced AT_1/AT_2 compounds compared to the conventional AT_1 selective compounds.

Acknowledgement : We wish to thank D.Annoot, J.-L. Fleury, F. François and A. Vermond for their technical assistance.

Notes and References

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(12) 5-keto tetrazole **27** was prepared from the corresponding 5-carboxyl imidazolyl biphenyl sulfonylurea[11] *via* the formation of the acyl chloride ($SOCl_2$, 55°C, overnight) followed by CuCN addition (2h in refluxing CH_3CN) and treatment of the resulting ketonitrile with Bu_3SnN_3 (overnight in refluxing xylene). Reduction of **27** with $NaBH_4$ in EtOH afforded **28**.

(*Received in Belgium* 2 *August* 1995; *accepted* 2 *October* 1995)