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DIHYDRO-IMIDAZOLONE DERIVATIVES AS ANGIOTENSIN II RECEPTOR ANTAGONISTS : CHIRAL EFFECT ON THE ACTIVITY

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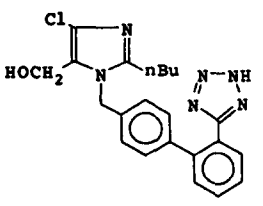
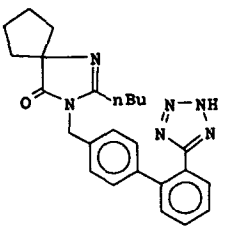
Abstract : The synthesis and structure activity relationship (SAR) of a series of appropriately substituted new dihydro-imidazolones with high affinity for the AT_1 Angiotensin II receptor are reported. This study emphasizes the importance of the configuration at the position 5 of the dihydro-imidazolone nucleus.

During the five past years, numerous potent nonpeptide Angiotensin II receptor antagonists have been reported which were expected to be effective in the treatment of hypertension. Among them, N-(biphenylylmethyl) imidazole derivatives[1] were found to produce antihypertensive effects upon oral administration in rodents, and one of them, DUP 753 (Losartan) is currently undergoing phase III clinical trial in human. We have previously reported that the imidazole could be advantageously replaced with the dihydro-imidazol-4-one nucleus[2]. However, like in the imidazole series, a methylbiphenyl carboxylic acid or better a methylbiphenyl tetrazole substituent linked to the position 3 of the heterocycle and a short alkyl chain at the position 2 of the imidazolone were needed for efficient receptor binding. SR 47436[2], a prototype compound in this new series actually displays very good oral activity in animal models and has undergone phase II clinical trial as antihypertensive agent. In this communication we report the synthesis and the SAR of antagonists bearing alkyl substituents at the position 5 of imidazolone nucleus[2,3].

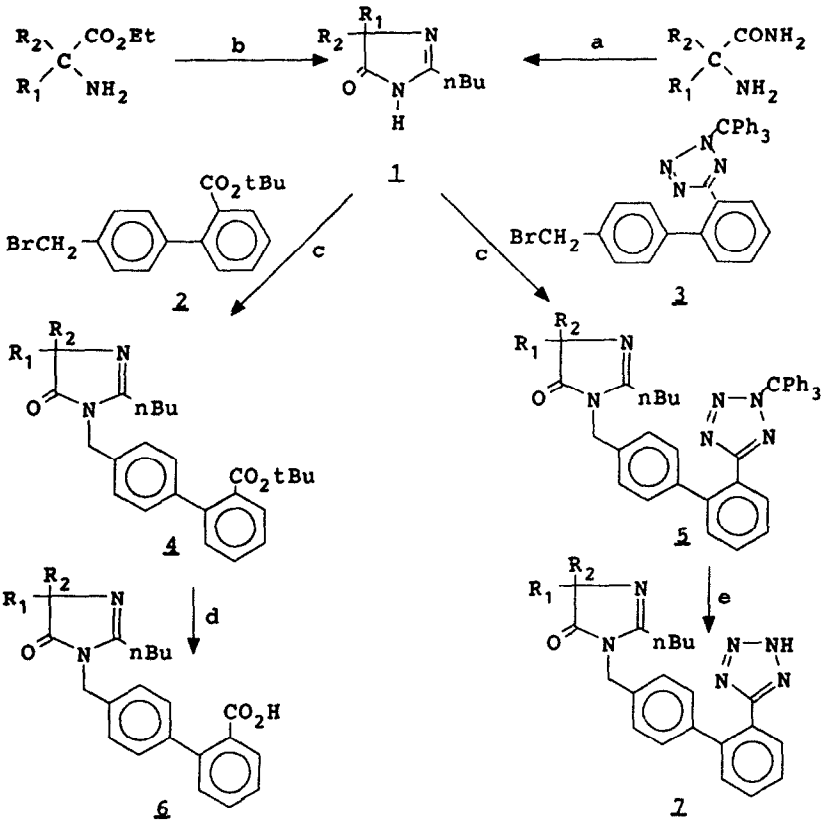


DUP 753



SR 47436

5,5-dialkyl dihydro-imidazolone derivatives were synthesized by the route described in scheme I. The key intermediate **1** was prepared from α-amino amide or α-amino ester, by cyclization with acyl chloride or imidate (pathway a and b respectively)[2,4,5]. Alkylation with bromo derivatives **2** or **3**, prepared as described by Carini et al.[1], led to the compounds **4** and **5** respectively. The position of alkylation was assessed by NMR experiments (Nuclear Overhauser Effect). After deprotection, compounds **4** and **5** afforded compounds **6** and **7** respectively.



SCHEME I

a) pathway a : nBu-COCl then KOH-MeOH; b) pathway b : nBu-C(=NH)OEt, xylene, few drops of AcOH; c) NaH, DMF; d) TFA; e) HCl

Compounds **6** were evaluated as AT_1 Angiotensin II receptor antagonists in vitro (i) in a radioligand binding assay involving displacement of [^{125}I]-Angiotensin II from a rat liver membranes preparation[6], (ii) in a functional assay involving the antagonism of the A II induced contraction of rabbit aortic tissue[6]. In some cases the in vivo inhibition of A II induced pressor response in conscious normotensive cynomolgus monkeys[6] was also evaluated.

The first part of this study was to synthesize compounds **6** with R_1=R_2 in order to determine the optimal size of subtituents at the position 5. Table 1 indicates that the presence of methyl groups affords the best results, bulkier substituents giving poor binding affinity and very weak antagonistic activity in the functional assay.

TABLE 1

SAR at the position 5 with symmetrical substitutions

Compound	R_1=R_2	Synthetic pathway	Binding on liver membranes* IC_{50} nM	Rabbit aortic rings* IC_{50} nM
6a	Methyl	b	35	120
6b	Ethyl	b	56	270
6c	n-Butyl	a	1700	4000
6d	Isobutyl	a	2100	5100
6e	Cyclopropyl	a	80	110

* : according to reference 6

We next turned our attention to compounds bearing two different substituents : a methyl group and a bulkier group[3]. For the initial evaluation, starting from racemic mixtures of amino acid derivatives, racemic dihydro-imidazolones were obtained. Table 2 shows that cyclopentyl and cyclohexyl group afforded the best results compared to either other alkyl groups or phenyl group. Compound **6 l** which bears an ethyl group instead of a methyl group is clearly less active than **6 g** (table 2). This compound was synthesized to ensure that our original choice of a methyl group for R_1 was justified.

TABLE 2

SAR at the position 5 with a methyl group

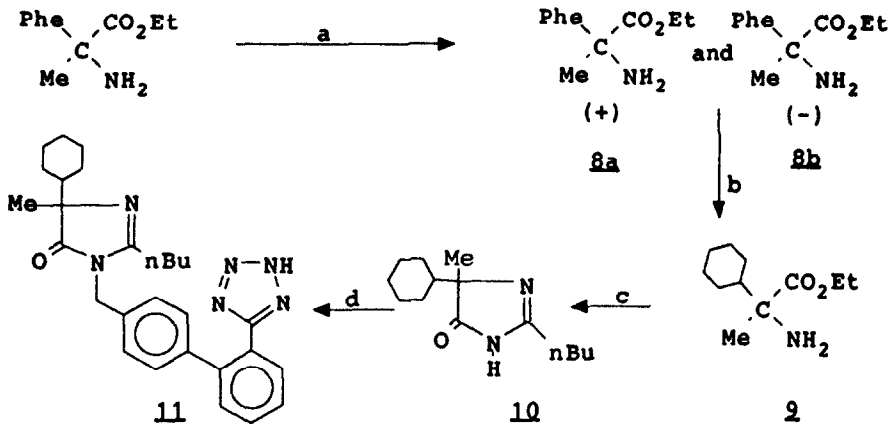
Compound	R_1	R_2	Synthetic pathway	Binding on liver membranes° IC_{50} nM	Rabbit aortic rings° IC_{50} nM
6f	Methyl	Cyclopentyl	a	3.3	9.6
6g	Methyl	Cyclohexyl	b	12	6.3
6h	Methyl	Isopropyl	a	7.3	16
6i	Methyl	Cyclopropyl	a	18	29
6j*	Methyl	2,4 dimethyl-pentyl	a	230	NT
6k	Methyl	Cyclohexylmethyl	b	150	NT
6l	Ethyl	Cyclohexyl	a	52	100
6m	Methyl	Phenyl	b	19	130

NT : not tested * : diastereoisomeric mixture
° : according to reference 6

These results taken all together, suggest that the affinity for the AT_1 Angiotensin II receptor appears to depend on interaction at two hydrophobic receptor subsites, a small one which fits with the methyl group and a large one which accommodates with the cyclohexyl group. According to this spatial dissymetry, we may anticipate that the

two enantiomers will behave differently. The two enantiomers **11a** and **11b** were then synthesized according to scheme II. The optical rotations of the intermediates and final products are shown in table 3.

SCHEME II



a) according to reference 7; b) according to reference 8; c) and d) according to scheme I.

TABLE 3

Optical rotations along the synthesis of 11a and 11b

	$[\alpha]_D$ (c=1, 20°C)			
Compound	**8**	**9**	**10**	**11**
a	+ 24.7 (EtOH)	+ 18 (EtOH)	- 57.2 ($CHCl_3$)	- 25.9 (MeOH)
b	- 25.5 (EtOH)	- 19.2 (EtOH)	+ 56.9 ($CHCl_3$)	+ 27.1 (MeOH)

The configuration at the carbon 5 of the dihydro-imidazolone is obviously the same as the configuration of the amino acid used for the synthesis. However, as absolute configuration of α-methylphenylglycine is not unquestionnable[9], the corresponding absolute configuration of **11a** and **11b** remains to be established. Biochemical data comparison of compounds **11a** and **11b** (table 4) clearly shows that the configuration at the carbon 5 greatly influences the affinity for AT_1 Angiotensin II receptor, the dextro isomer (**11b**) being about 20 times more active than the levo isomer (**11a**).

TABLE 4

Chiral effect at the position 5

Compound	Binding* on liver membranes IC_{50} nM	Rabbit aortic rings* IC_{50} nM
11a	110	NT
11b	5.2	0.77

NT : not tested * : according to reference 6

It as been previously reported[1] in the imidazole series that substitution of the carboxylic function of biphenyl group by the tetrazole nucleus increases the potency and the duration of the oral activity. Racemic compounds **7a** (R_1= Methyl, R_2= Cyclopentyl) and **7b** (R_1= Methyl R_2= Cyclohexyl) were synthesized according to scheme I in order to compare their activity with those of the corresponding carboxylic derivatives **6f** and **6g** (table 2).

TABLE 5

Effect of the tetrazole moiety on the activity

Compound	R1	R2	Binding[a] on liver membranes IC_{50} nM	Rabbit aortic rings[a] IC_{50} nM
7a	Methyl	Cyclopentyl	7.6	3.1
7b	Methyl	Cyclohexyl	4.6	2.7

a : according to reference 6

Table 5 summarizes the results obtained in vitro : the beneficial effect of the tetrazole doesn't seem as important as in the imidazole series in terms of affinity. Nevertheless, in vivo, at least for 7b, in the model of Angiotensin II induced pressor effect in cynomolgus monkeys[6], the tetrazole led to a significant improvement (figure 1) in terms of onset of activity and duration of action.

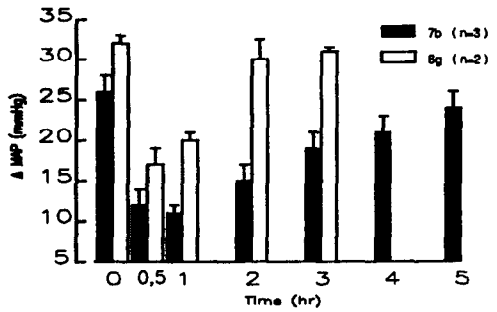


Figure I. Comparative inhibitory effects of 7b and 6g at 3mg/kg p.o. on the pressor response to AII (100 ng/kg, i.v.) in conscious normotensive cynomolgus monkeys.

The AII receptor antagonists reported here greatly differ structurally from previously described imidazole antagonists such as DUP 753. Despite these differences, all the biochemical and pharmacological data have clearly shown that dihydro-imidazolone nucleus should be justifiably considered as a candidate template in the general design of nonpeptide AT_1 Angiotensin II receptor antagonists. Moreover, stereoselectivy at the position 5 carbon offered new insights in the knowledge of the tridimensionnal model of the receptor binding site.

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References and Notes

1. Carini, D. J.; Duncia, J.V.; Aldrich, P.E.; Chiu, A.T.; Johnson, A.L.; Pierce, M.E.; Price, W.A.; Santella III, J.B. Wells, G.J.; Wexler, R.R.; Wong, P.C.; Yoo, S.E.; Timmermans, P.B.M.W.M. *J. Med. Chem.* **1991**, *34*, 2525.
2. (a) Bernhart, C.; Breliere, J.C.; Clément, J.; Nisato, D.; Perreaut, P. *European patent 454511.*

   (b) Bernhart, C.A.; Perreaut, P.M.; Ferrari, B.P.; Muneaux, Y.A.; Assens, J L.,A.; Clément, J.; Haudricourt, F.; Muneaux, C.F.; Taillade, J.E.; Vignal, M.A.; Gougat, J.; Guiraudou, P.R.; Lacour, C.A.; Roccon, A.; Cazaubon, C.F.; Breliere, J.C.; Le Fur, G.; Nisato, D. *Submitted for publication.*
3. Perreaut, P.; Muneaux, C.; Muneaux, Y. *European patent 532410.*
4. Jacquier, R.; Lacombe, J.M.; Maury, G. *Bull.Soc. Chim. Fr.* **1971**, 1040.
5. Takenaka, H.; Hayase, Y. *Heterocycles* **1989**, *29*, 1185.
6. Cazaubon, C.; Gougat, J.; Bousquet, F.; Guiraudou, P.; Gayraud, R.; Lacour, C.; Roccon, A.; Galindo, G.; Barthélémy, G.; Gautret, B.; Bernhart, C.; Perreaut, P.; Breliere, J.C.; Le Fur, G.; Nisato, D.

   J. Pharmacol. Exp. Ther. **1993**, *265*, 826.
7. Sugi,Y.; Mitsui, S. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 2984.
8. (a) Dahn, H.; Garbarino, J.A.; O'Murchu, C. *Helv. Chim. Acta* **1970**, *53*, 1370.

   (b) Bonner, W.A.; Zderic, J.A. *J.Am. Chem. Soc.* **1956**, *78*, 3218.
9. (a) Mizuno, H.; Terashima, S.; Achiwa, K; Yamada, .S.I. *Chem. Pharm.Bull.* **1967**, *15*, 1749.

   (b) Hartwig, W.; Schöllkopf, U. *Liebigs Ann. Chem.* **1982**, 1952.

   (c) Kruizinga, W.H.; Bolster, J.; Kellogg, R.M.; Kamphuis, J.; Boesten, W H.J.; Meijer, E.M.; Shoemaker, H.E. *J. Org. Chem.* **1988**, *53*, 1826.

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