Bioorganic & Medicinal Chemistry Letters, Vol. 4, No. 1, pp. 157-162, 1994
Printed in Great Britain

0960-894X/94 $6.00 + .00

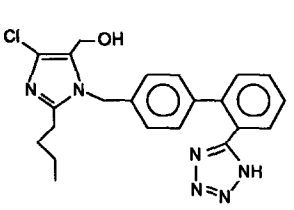
CYCLOPENTANESPIRO-3H-DIHYDRO-PYRIMIDINONES AS ANGIOTENSIN II AT_1 RECEPTOR ANTAGONISTS

C.A. Bernhart*, F.B. Haudricourt, J.L. Assens, J. Gougat, C. Lacour, A. Roccon, C. Cazaubon, J.C. Brelière, G. Le Fur and D. Nisato

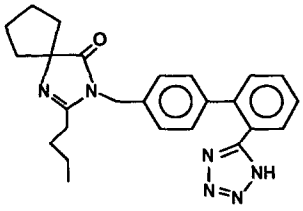
SANOFI Recherche, 371, rue du Professeur J. Blayac, 34184 Montpellier Cedex 4 - France

Abstract : A novel series of substituted 3H-dihydro-pyrimidinones, homologues of SR 47436, was identified as AT_1 receptor antagonists. The best compounds showed high affinity for the AT_1 receptor (rat liver membrane preparation) with IC_{50}'s in the nanomolar range. Active p.o. in rats in an AII infused model, they are inactive in cynomolgus monkeys.

Angiotensin II (AII) is a powerful vasoconstricting agent, produced by the Renin-Angiotensin System (RAS)[1]. Angiotensin converting enzyme inhibitors block the conversion of AI to AII. Direct antagonism of AII binding at its receptor is potentially a more selective method of interfering with the RAS. Losartan (DuP 753) was the first representative of this new class of non-peptide AT_1 receptor antagonists[2]. Following our own strategy we have designed a new series of dihydro-imidazolones which are potent and selective AT_1 antagonists[3,4]. SR 47436 the most active compound of this series is now undergoing phase II clinical trials.



DuP 753

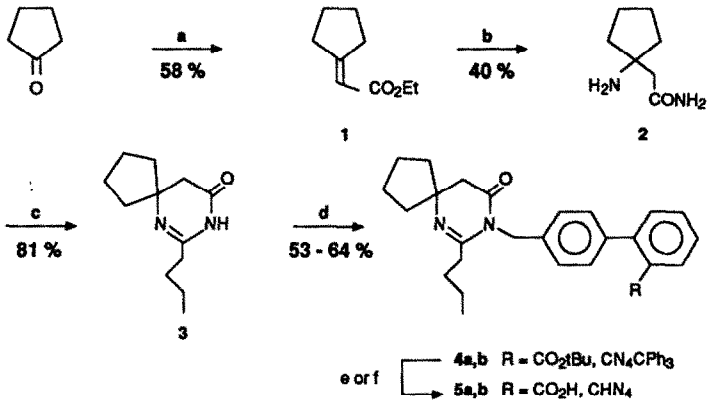


SR 47436

The replacement of the imidazole ring in DuP 753 by our dihydro-imidazolone gave mainly positive results. It was then tempting to explore the potential of its six member ring homologue. Two 3H-dihydro-pyrimidinones can be produced from SR 47436 : the first by insertion of a methylene between the carbonyl and the spirocyclopentane ring and the second between the spirocyclopentane and the nitrogen.

The synthesis of these compounds is outlined in schemes 1-3. Cyclopentanone was treated with triethyl phosphonoacetate to yield **1**, which on heating with ammonia at 150°C produced the desired amino-amide **2**. Cyclisation to the dihydro-pyrimidinone **3** occurred by treatment with trimethyl orthovalerate. Alkylation of **3** with the appropriate 4-bromomethyl-biphenyl led to a single isomer due to steric hindrance of the spirocyclopentane ring.

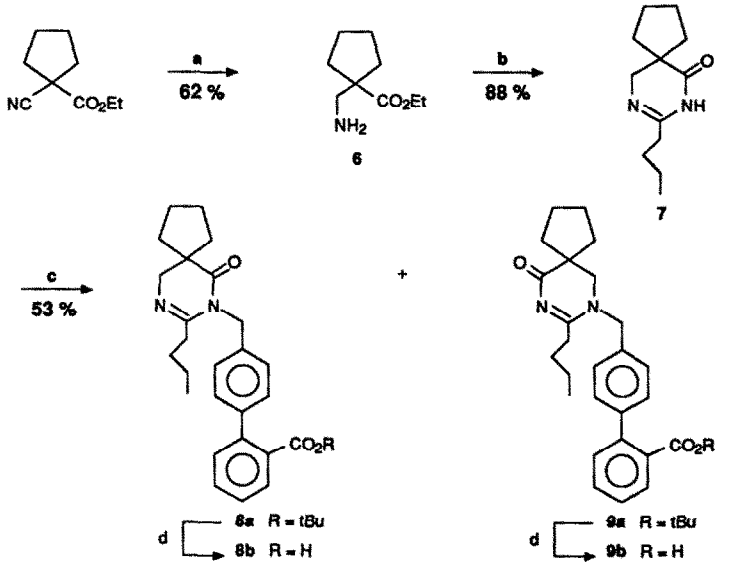
Scheme 1



a. $(EtO)_2POCH_2CO_2Et/NaH/C_6H_6$ - **b.** $NH_3/150°C$ - **c.** $C_4H_9C(OMe)_3/AcOH/100°C$ - **d.** $R\text{-}C_6H_4\text{-}C_6H_4\text{-}CH_2Br/NaH/DMF/25°C$ - **e.** TFA/CH_2Cl_2 - **f.** HCl 10%/CH_3OH.

The second dihydro-pyrimidinone bearing the spirocyclopentane in position α in relation to the carbonyl was prepared starting from ethyl 1-cyano-cyclopentane carboxylate.

Scheme 2

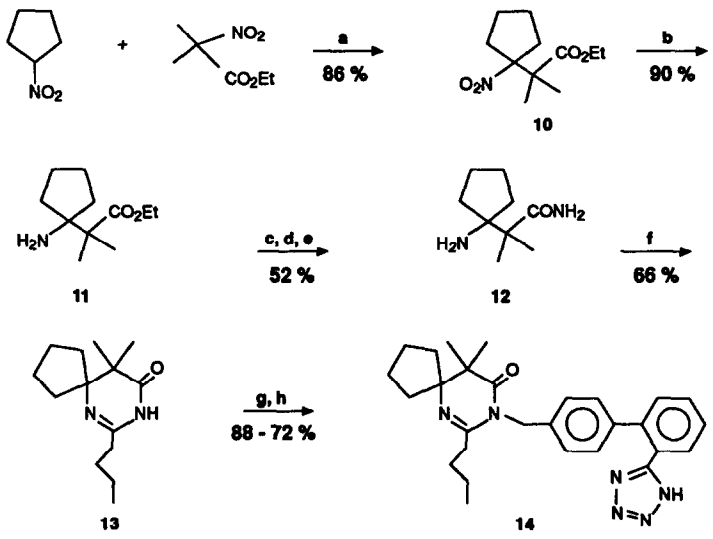


a. $H_2/Rh\text{-}Al_2O_3$ 5%/NH_3/EtOH - **b.** $C_4H_9C(=NH)OEt$/Xylene/AcOH/Reflux - **c.** $CO_2tBu\text{-}C_6H_4\text{-}C_6H_4\text{-}CH_2Br/NaH/DMF$ - **d.** TFA/CH_2Cl_2.

The nitrile was reduced by hydrogenation over Rh/Al_2O_3. On treatment with ethyl valerimidate, **6** cyclised to the dihydro-pyrimidinone **7**. In this case alkylation yielded the two regioisomers as the spirocyclopentane is unable to exert any steric hindrance on the two potential alkylation positions. The structure of each isomer was established by NMR-NOE[5].

As the dihydro-pyrimidinone ring offered a supplementary substitution position we also synthesized a fully substituted compound **14**. Displacement of the nitro group from ethyl 2-methyl-2-nitro-proprionate by the potassium salt of nitrocyclopentane furnished **10** with excellent yield. The nitro group was reduced by hydrogenation over Pd/C to yield **11**.

Scheme 3

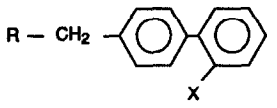


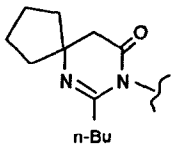
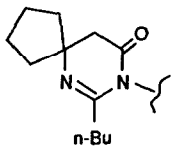
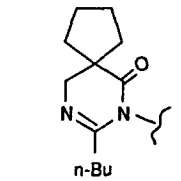
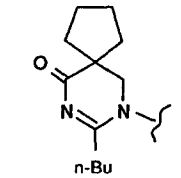
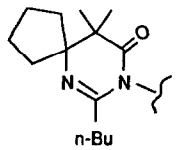
a. t-BuOK/DMSO/hν - **b.** H_2/Pd-C 10 % - **c.** NaOH - **d.** $SOCl_2$/Reflux - **e.** NH_4OH 20 % - **f.** $C_4H_9C(OMe)_3$/AcOH/160°C - **g.** (CN_4CPh_3)-C_6H_4-C_6H_4-CH_2Br/NaH/DMF/25°C - **h.** HCl 10 %/CH_3OH.

Compound **12** could not be obtained directly from **11** by aminolysis and was thus synthesized via the carboxylic acid chloride. The dihydro-pyrimidinone was finaly obtained by heating **12** at 160°C in trimethylorthovalerate under acid catalysis. Alkylation with NaH in DMF again yielded only one isomer.

The binding data for the target compounds are shown in Table 1. These were generated from a rat liver membrane preparation which has been recognized to be specific for AT_1 receptor subtype[6]. The position of the spirocyclopentane ring in relation to the carbonyl would not seem to be pivotal as the activity was only slightly higher for **5a** bearing the ring in position ß. Comparison of compounds **8b** and **9b** highlighted the crucial position of the carboxy-biphenyl moiety towards the carbonyl. Optimal activity was reached with the two groups close together.

Table 1 : Inhibition of AII-receptor binding



Compound	R	X	IC_{50} (nM)[7]
5a		CO_2H	53
5b		CHN_4	1.0
8b		CO_2H	71
9b		CO_2H	1300
14		CHN_4	2.2
SR 47436			1.3

In the most active compound the replacement of the carboxy group by the tetrazole led to a large activity increase (**5b** versus **5a**). Introduction of two methyl groups between the spirocyclopentane ring and the carbonyl resulted in a slight activity decrease due to the limited size of the lipophilic pocket which accomodates the spirocyclopentane.

The antihypertensive activity of compound **5b** was evaluated in two AII-infused animal models (rat and cynomolgus monkeys)[8]. **5b** was equipotent compared to SR 47436 in rat, (Fig. 1) but was inactive in cynomolgus monkey (Fig. 2)[9]. Compound **14** in which the position α to the carbonyl (a possible metabolic sensitive position) was blocked by two methyl groups was like **5b** in that it was inactive in the cynomolgus monkey model.

Figure 1 : Comparative inhibitory effects of SR 47436 and 5b at 3 mg/kg p.o. on the pressor response to AII (40 ng/kg, i.v.) in conscious normotensive rats

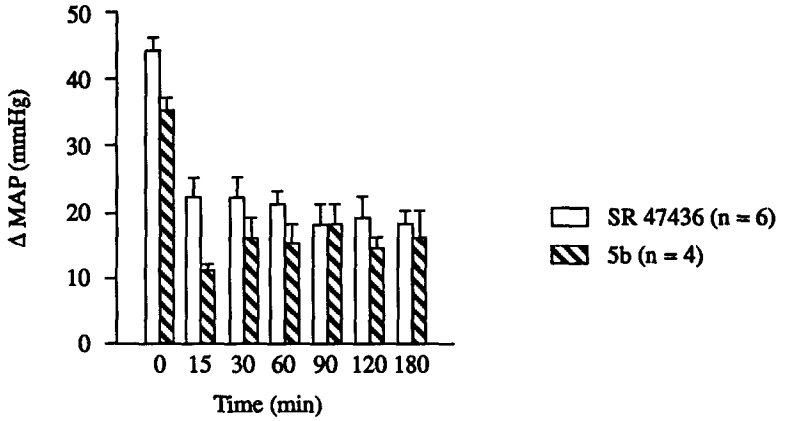
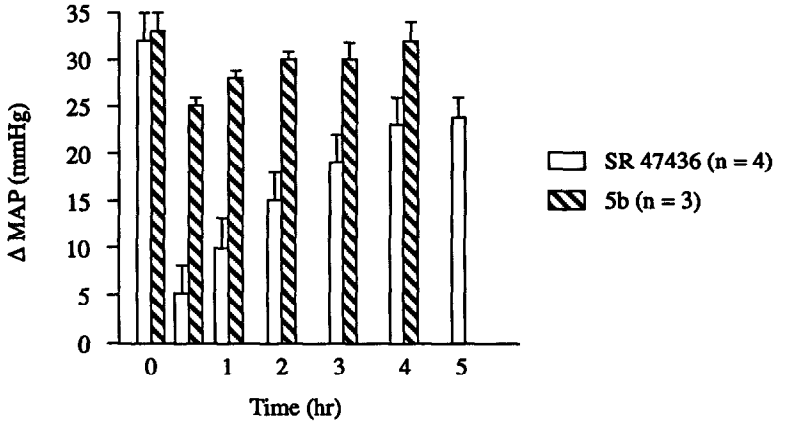


Figure 2 : Comparative inhibitory effects of 5b and SR 47436 at 3 mg/kg p.o. on the pressor response to AII (100 ng/kg, i.v.) in conscious normotensive cynomolgus monkeys



The poor absorption in cynomolgus monkeys of the dihydro-pyrimidinone series compared to the imidazolones has yet to be explained ; but perhaps a rapid degradation in the liver might explain the lack of oral activity[10]. Because of this important limitation, this series of compounds has not been taken in consideration for further development.

References and Notes

1. Peach, M.J., *Biochem. Pharmacol.* **1981**, 30, 2745.

2. 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, 2525-2547.

3. Bernhart, C.A., Perreaut, P.M., Ferrari, B.P., Muneaux, Y.A., Assens, J.L.A., Clément, J., Haudricourt, F., Muneaux, C.F., Taillades, J.E., Vignal, M.A., Gougat, J., Guiraudou, P., Lacour, C.A., Roccon, A., Cazaubon, C.F., Brelière, J.C., Le Fur, G., Nisato, D., *Submitted for publication in J. Med. Chem.*

4. Cazaubon, C., Gougat, J., Bousquet, F., Guiraudou, P., Gayraud, R., Lacour, C., Roccon, A., Galindo, G., Barthelemy, G., Gautret, B., Bernhart, C., Perreaut, P., Brelière, J.C., Le Fur, G., Nisato, D., *J. Pharmacol. Exp. Ther.* **1993**, 265, 826-834.

5. Assignments were made by NOE enhancements between the benzylic methylene and the cyclic methylene in **9a**. No such enhancement was seen in **8a**.

6. The binding experiments were performed as described in ref. 4.

7. IC_{50} designates 50 % inhibition of specific binding of [^{125}I] AII.

8. Inhibition of the AII induced pressor response in conscious normotensive rats and conscious normotensive cynomolgus monkeys were performed as described in ref. 4.

9. The slight inhibition observed for **5b** is not statistically significant relative to the control response.

10. In cynomolgus monkeys, **5b** and **14** inhibited the AII induced hypertension when administrated intravenously at 0.3 mg/kg. Like for **SR 47436** maximum activity was reached (**5b** : - 56 % ; **14** : - 61 % ; **SR 47436** : - 67 %) after 15 minutes and lasted for 1 h.

(*Received* 22 *July* 1993; *accepted* 27 *August* 1993)