Bioorganic & Medicinal Chemistry Letters, Vol. 4, No. 1, pp. 29-34, 1994
Printed in Great Britain

0960-894X/94 $6.00 + .00

VALSARTAN, A POTENT, ORALLY ACTIVE ANGIOTENSIN II ANTAGONIST DEVELOPED FROM THE STRUCTURALLY NEW AMINO ACID SERIES

Peter Bühlmayer*, Pascal Furet, Leoluca Criscione, Marc de Gasparo, Steven Whitebread, Tibur Schmidlin, René Lattmann and Jeanette Wood
Research Department, Pharmaceuticals Division
Ciba-Geigy Ltd., P.O. Box, CH-4002 Basel, Switzerland

Abstract: Starting from the structure of DuP-753 and a 3-dimensional model of the pentapeptide Tyr-Ile-His-Pro-Ile, a series of new and highly potent antagonists has been designed where the imidazole moiety of the Du Pont compound has been replaced by an N-acylated aminoacid residue. VALSARTAN (Ex. **4e**, CGP48933, (S)-N-Valeryl-N-{[2'-(1H-tetrazol-5-yl-)biphenyl-4-yl]methyl}-valine), has been selected for clinical investigation.

Introduction

The renin angiotensin system (RAS) produces Angiotensin II (Ang II), a very potent vasoconstrictive and volume-retaining hormone which is partly responsible for regulation and maintenance of blood pressure.[1] Blockers of the RAS such as angiotensin converting enzyme (ACE) inhibitors have successfully been introduced into the market for the treatment of hypertension and congestive heart failure.[2a,b] However, blocking the system with specific antagonists of Ang II may turn out to be a more suitable way for blood pressure control. Recently nonpeptidic, orally active antagonists have been discovered by the group at Du Pont.[3a,b] Losartan (DuP-753, 2-n-Butyl-4-chloro-5-hydroxymethyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-imidazole potassium salt, see Table 1) is the most advanced clinical candidate in the field (phase III).

Concept

Many replacements of the imidazole part of the Du Pont compound by other heterocycles have been published in literature and patents.[4a,b] In contrast, we have designed a novel series of orally active derivatives in which the heterocycle of losartan has been replaced by an acylated aminoacid. We speculated that the imidazole mimics a peptide bond and the tetrazole mimics the C-terminal carboxylic function of Ang II. Considering the importance of the butyl chain in losartan,[3a,b] the following hypothesis was postulated: The butyl group mimics the side chain of Ile(5) in Ang II which implies that the imidazole ring of the nonpeptidic compound might be a substitute for the amide bond located between Ile(5) and His(6). Extensive comparative analyses of energy minimized conformations of losartan and the C-terminal pentapeptide Tyr-Ile-His-Pro-Ile of [Sar(1),Ile(8)]Ang II were undertaken to check this idea.[5a-f] The study lead to the satisfactory overlap of the two molecules shown in Fig.

1a, which encouraged us to work along this hypothesis. Accordingly, with the intention to mimic His(6), we started our synthetic program using an aromatic amino acid (**4b**).

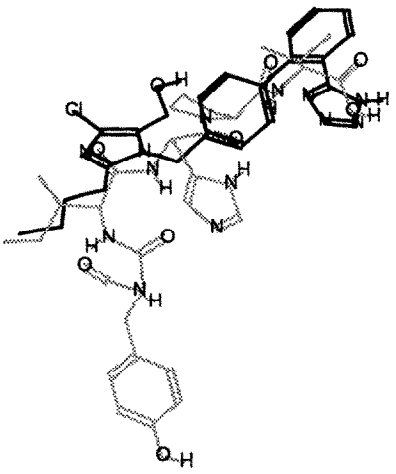


Fig. 1a: Superposition of losartan (bold) with the C-terminal pentapeptide part of [Sar(1),Ile(8)]Ang II. The butyl imidazole group of losartan mimics residue Ile(5) while the phenyl-tetrazole matches the C-terminal amino acid.

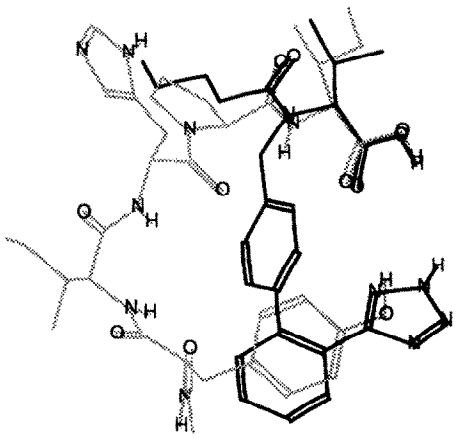


Fig. 1b: Superposition of valsartan (bold) with the C-terminal pentapeptide part of [Sar(1),Ile(8)]Ang II (modified hypothesis). The butyl chain and the phenyl-tetrazole moiety correspond to the side chains of Pro(7) and Tyr(4) respectively.

Synthesis of amino acid derivatives

Starting from the biphenylbromomethylnitrile **A**[3a] (Fig. 2) aminoacid esters were alkylated under standard conditions. Subsequently the secondary amines **1** were acylated in the presence of Hünig's base. Treatment of the acylated intermediates **2** with tributyl tin azide[3a] in refluxing xylene gave the esters **3**. Cleavage of the esters **3** by either aqueous base (methylester) or by hydrogenation (benzylester) in the presence of palladium on active carbon yielded the free amino acid derivatives **4**. The primary amide **5** was produced by activation of **4e** with N-Ethyl-N'-(3-dimethylaminopropyl)-carbodiimid-hydrochloride (EDC) followed by addition of ammonia in dimethylformamide. The alcohol **6** was obtained by reduction of **3** (methylester) with lithiumborohydride.

Results

The results were obtained following the methods described by Criscione et al.[6] and are listed in Table 1. From the data shown it can be seen that compound **4e** has the best activities *in vitro* and *in vivo*. The compounds **4c**, **4e**, **5** and **6** inhibited Ang II - induced pressor response in the pithed rat model after oral administration (10 mg/kg) and were further evaluated for their antihypertensive activity in the renal hypertensive rat[6] (RHR, 2K1C). At doses of 10 mg/kg and less, valsartan (**4e**) has the best potency, efficacy and longest duration of action (up to 24 hrs.). Valsartan also showed hypotensive activity in the conscious, sodium-depleted marmoset[6] at a dose of 30 mg/kg (up to 24 hrs.). In all tests losartan has been used as standard for comparison. The

antihypertensive effects of valsartan and losartan in conscious, restrained RHR and freely moving marmosets are presented in Fig. 3.

Fig. 2: Synthesis of aminoacid-derived Ang II antagonists

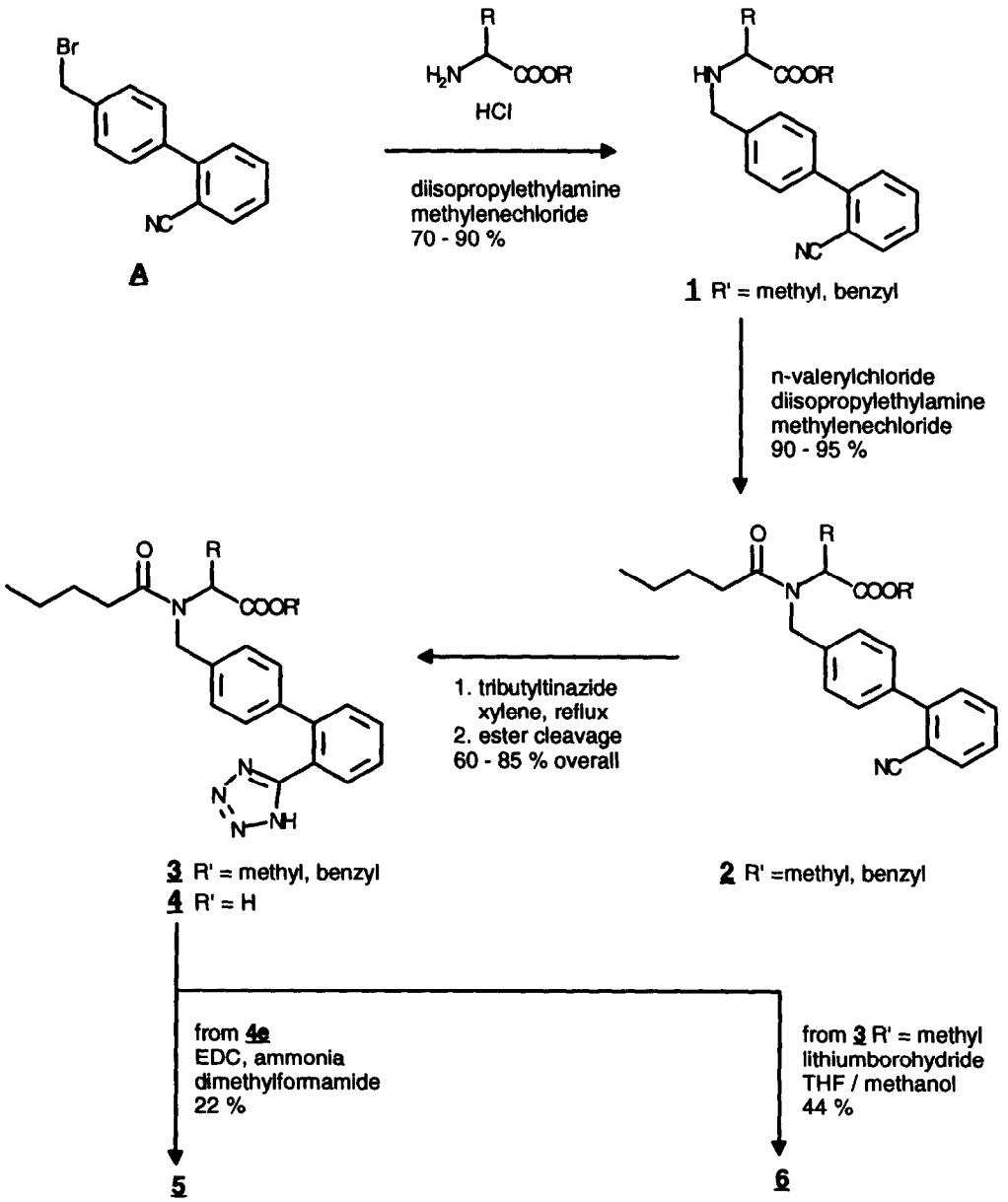
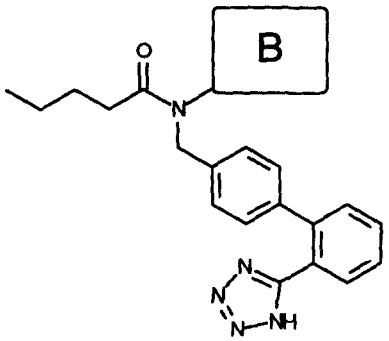
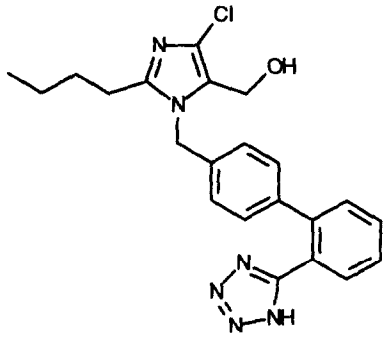


Table 1: Pharmacological characterization of aminoacid type Ang II antagonists[6]



aminoacid type series



losartan (DuP-753, potassium salt)

Example	stereo-chem.	B *	IC_{50} µM AT_1 (assays in absence of BSA **)	IC_{50} µM rabbit aorta, inhib.of Ang II press. resp.	pithed rat % inhib. of Ang II press. resp. at 10 mg/kg po
losartan			0.008	0.024	50
3	S	-CH[CH(CH$_3$)$_2$]COOCH$_3$	0.06	0.068	10
4a		-CH$_2$COOH	0.6	not tested	not tested
4b	R/S	-CH(CH$_2$-C$_6$H$_4$-p-F)COOH	0.03	0.14	not tested
4c	S	-CH(CH$_3$)COOH	0.024	0.011	33
4d	R	-CH(CH$_3$)COOH	0.2	0.104	6 (30 mg/kg)
4e valsartan	S	-CH[CH(CH$_3$)$_2$]COOH	0.0027	0.0014	97
4f	R	-CH[CH(CH$_3$)$_2$]COOH	0.3	0.1	5
4g	S	-CH(CH$_2$C$_6$H$_{11}$)COOH	0.06	0.5	not tested
5	S	-CH[CH(CH$_3$)$_2$]CONH$_2$	0.006	0.003	81
6	S	-CH[CH(CH$_3$)$_2$]CH$_2$OH	0.27	0.068	72 (30 mg/kg)

* satisfactory analytical data for all compounds have been obtained (NMR, HR FAB-MS)
** bovine serum albumine

Fig. 3a: Antihypertensive effects of valsartan (●) and losartan (■) in restrained RHR (10 mg/kg po)

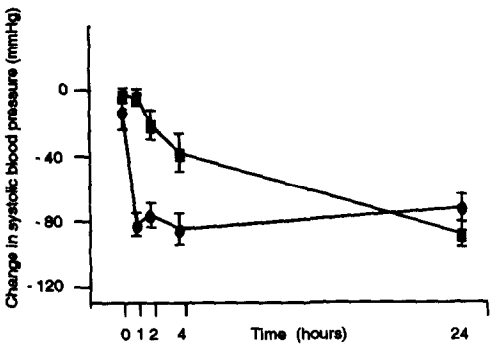
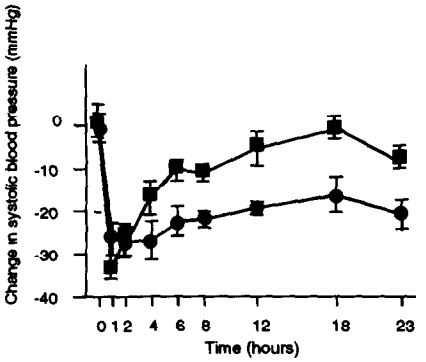


Fig. 3b: Antihypertensive effects of valsartan (●) and losartan (■) in freely moving marmosets (30 mg/kg po)



Discussion

From the *in vitro* data shown in table 1 it can be seen that the nature of the amino acid side chain is crucial for activity. However, based on our hypothesis (Fig. 1a), we did not expect that both, aromatic (mimic of His[6]) as well as aliphatic side chains, would be tolerated. Analogues with (S)-stereochemistry are substantially more active than their corresponding (R)-enantiomers (Ex. **4c/4d**, **4e/4f**). High potency was achieved with several compounds derived from aliphatic amino acids. Therefore these examples are preferred in our series. The results of compounds **5** and **6** demonstrate that good activity can also be achieved with amides and, to a lesser extent, with alcohols. In peptides such as [Sar(1),Ile(8)]Ang II it has been shown that the nature of the side chains in residues Tyr(5) (phenolic)[7a,b] and Ile(8) (aliphatic)[8a,b] is important for modulation of functional properties. Taking into account these aspects we have modified our hypothesis as follows: The amide moiety of valsartan mimics the C-terminus and the phenyl-tetrazole part mimics the phenol moiety of Tyr(4) of Ang II (Fig. 1b). In this superposition the pentapeptide is shown in a U-shaped conformation whereas in Fig. 1a an extended conformation has been used. A related model has been proposed for the first imidazole series[3] and for the imidazole-acrylic acid series[9]. In RHR valsartan has a faster onset of action than losartan. In marmosets however, the two compounds behave similarly in that respect. These findings may be due to a different metabolism of losartan in the two species.[6] In marmosets valsartan has a longer duration of action than losartan. Valsartan has a unique structure compared to all other Ang II antagonists and is currently undergoing clinical investigation.

Acknowledgment

The excellent technical work of Markus Müller, Raymond Baudet, Michele Mele, Dominique Monna, Helene Thomann, Christian Schnell and Peter Forgiarini is gratefully acknowledged.

References and Notes

1 Sealey, J.E.; Laragh, J.H. Hypertension: *Pathophysiology, Diagnosis and Management*, Laragh, J.H.; Brenner, B.M., Eds.; Raven: New York, **1990**; p. 1287.

2 a) Consensus Trial: The Consensus Trial Study Group *N. Engl. J. Med.* **1987**, *316*, 1429.
b) Waeber, B.; Nussberger, J.; Brunner, H.R. *Hypertension: Pathophysiology, Diagnosis and Management*, Laragh, J.H.; Brenner, B.M., Eds.; Raven: New York, **1990**; p. 2209.

3 a) 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.; Timmermans, P.B.M.W.M. *J. Med. Chem.* **1991**, *34*, 2525.
b) Duncia, J.V.; Carini, D.J.; Chiu, A.T.; Johnson, A.L.; Price, W.A.; Wong, P.C.; Wexler, R.R.; Timmermans, P.B.M.W.M. *Medical Research Reviews*, **1992**, *12*, 149 and references cited therein.

4 a) Bühlmayer, P. *Current Opinion in Therapeutic Patents* **1992**, *2*, 1693.
b) Dudley, T.D.; Hamby, J.M. *Current Opinion in Therapeutic Patents* **1993**, *3*, 581.

5 Molecular modelling methods used:
a) CONCEPTOR: In house molecular modelling program written by Cohen, N.C.; similar to SCRIPT: Cohen, N.C.; Colin, P.; Lemoine, G. *Tetrahedron* **1981**, *37*, 1711.
b) Still, W.C.; Mohamadi, F.; Richards, N.G.J.; Guida, W.C.; Liskamp, R.; Lipton, M.; Caufield, C.; Hendrickson, T.; *BATCHMIN V2.0*; Department of Chemistry, Columbia University: New York.
c) For the NCC force field, see: Academic Press, New York, **1985**; Vol. 14, p. 50 and references cited therein.
d) Gibson, K.D. and Scheraga, H.A. *J. Comp. Chem.* **1987**, *8*, 826.
e) Still, W.C.; Mohamadi, F.; Richards, N.G.J.; Guida, W.C.; Liskamp, R.; Lipton, M.; Caufield, C.; Hendrickson, T. *MACROMODEL V2.0*; Department of Chemistry, Columbia University, New York.

6 Criscione, L.; de Gasparo, M.; Bühlmayer, P.; Whitebread, S.; Ramjoué, H.; Wood, J. *Br. J. Pharmacol.*, **1993**, in press.

7 a) Scanlon, M.N.; Matsoukas, J.M.; Franklin, K.J.; Moore, G.J. *Life Sciences* **1984**, *34*, 317.
b) Goghari, M.H.; Franklin, K.J.; Moore, G.J. *J. Med. Chem.* **1986**, *29*, 1121.

8 a) Hsieh, K.; Jorgensen, E.C. *J. Med. Chem.* **1979**, *22*, 1038.
b) Hsieh, K.; Needleman, P.; Marshall, G.R. *J. Med. Chem.* **1987**, *30*, 1097.

9 Weinstock, J.; Keenan, R.M.; Samanen, J.; Hempel, J.; Finkelstein, J.A.; Franz, R.G.; Gaitanopoulos, D.E.; Girard, G.R.; Gleason, J.G.; Hill, D.T.; Morgan, T.M.; Peishoff, C.E.; Aiyar, N.; Weidley, E.F.; Edwards, R.M. *J. Med. Chem.* **1991**, *34*, 1514.

(*Received* 24 *August* 1993; *accepted* 15 *September* 1993)