Registry No. 1 (X = Y = F), 108966-71-8; 1 (X = Br, Y = H), 701-34-8; 1 (X = Cl, Y = H), 98-64-6; 1 (X = Cl, Y = CO₂CH₃), 61508-36-9; 1 (X = Cl, Y = H), 29619-30-5; 2 (X = Br, Y = H), 29619-31-6; 2 (X = Cl, Y = H), 29619-30-5; 2 (X = Cl, Y = CO₂CH₃), 108966-63-8; 3a, 108966-48-9; 3b, 108966-49-0; 3c, 108966-51-4; 3d, 108966-55-8; 3e, 108966-50-3; 3f, 108966-53-6; 3g, 108966-76-9; 3h, 135832-41-6; 3i, 135832-42-7; 3j, 108966-54-7; 3k, 108966-70-3; 3l, 108966-75-2; 3q, 108966-76-3; 3n, 108966-74-1; 3o, 108966-70-2; 3t, 108966-75-2; 3q, 108966-78-5; 3r, 108966-75-1; 3s, 108966-65-2; 3t, 108966-60-5; 3t, 108966-65-3; 3t, 108966-65-3; 3t, 108966-65-3; 3t, 108966-65-5; 3t, 108966-65-7; 3t, 108966-65-7; 3t, 108966-65-7; 3t, 108966-65-7; 3t, 108966-66-7; 3t,

5b, 104438-09-7; **6a**, 104437-96-9; **6b**, 104438-00-8; **6c**, 135832-36-9; **6d**, 104437-99-2; **6e**, 104438-02-0; **6f**, 104438-04-2; **6g**, 104438-05-3; **6h**, 135832-37-0; **6i**, 135832-38-1; **6j**, 135832-39-2; **6k**, 135832-40-5; **9a**, 122-97-4; **9b**, 122-72-5; **9c**, 3360-41-6; **9d**, 7492-40-2; **9e**, 10521-91-2; **9f**, 75553-28-5; **10a**, 135832-46-1; **10b**, 135832-47-2; **10c**, 135832-48-3; **10d**, 135832-49-4; **10e**, 135832-50-7; **10f**, 135832-51-8; **11**, 452-66-4; **12a**, 71916-91-1; **12b**, 135865-35-9; **12c**, 135832-54-1; **13a**, 135832-55-2; **13b**, 135832-56-3; **13c**, 135832-57-4; **20**, 105951-30-2; **22**, 96803-89-3; **23**, 96803-92-8; **1**, 2-difluorobenzene, 367-11-3; chlorosulfonic acid, 7790-94-5; isobutylamine, 78-81-9; 2-mercaptoethanol, 60-24-2; 3-mercaptopropanol, 19721-22-3; diethyl malonate, 105-53-3.

Nonpeptidic Angiotensin II Antagonists: Synthesis and in Vitro Activity of a Series of Novel Naphthalene and Tetrahydronaphthalene Derivatives

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Starting from the structure of the novel nonpeptidic angiotensin II antagonist DuP 753, a series of more rigid analogues was prepared by replacing the biphenyl part of DuP 753 with a naphthalene ring. Five different regioisomers (compounds 6a-e) were synthesized, and receptor binding in rat smooth muscle cell preparations as well as inhibition of angiotensin II induced contraction of rabbit aortic rings was measured and the order of potency was compared with predictions made on the basis of a molecular modeling study. In good agreement with the predictions, the 2,6-substituted regioisomer 6d and its analogue 7 (isomeric at the imidazole substituent) were found to be most potent, but were still weaker than DuP 753. Tetrahydronaphthalene derivatives with and without an additional methyl group in the α -position to the acidic function and with this same 2,6-substitution pattern (compounds listed in Table III) were then prepared with the expected potency range, surprisingly no further potency increase was observed after replacement of the carboxylic acid function by a tetrazole (compounds 18a,b). These results may indicate that the compounds do not bind to the AT₁ receptor in the same way as DuP 753.

Introduction

The search for angiotensin II antagonists as potential antihypertensive agents started more than 20 years ago and many peptidic antagonists have been described in the literature.¹ The recent discovery of nonpeptidic antagonists $(I)^2$ and the subsequent successful optimization of this



I (S-8307; Takeda)

II (DuP 753; Du Pont)

initial lead $(II)^3$ has however opened up a completely new field in angiotensin II (AII) antagonist research,^{4,5} and

- See, for example: Bumpus, F. M.; Koshla, M. C. Hypertension, Physiopathology and Treatment; Genest, J., Koiw, E., Kuchal, O., Eds.; McGraw Hill: New York, 1977; pp 183-207.
- (2) Furukawa, Y.; Kishimoto, S.; Hishikawa, R. Hypotensive imidazole-5-acetic acid derivatives. U.S. Patent 4,355,040, issued to Takeda Chemical Industries Ltd., Osaka, Japan, 1982.
- (3) Carini, D. J.; Duncia, J. J. V. Eur. Pat. Appl. 253 310, 1988, issued to Du Pont de Nemours and Co. Inc., Wilmington, DE.
- (4) Duncia, J. V.; Chiu, A. T.; Carini, D. J.; Gregory, G. B.; Johnson, A.; Price, W. A.; Wells, G. J.; Wong, P. C.; Calabrese, J. C.; Timmermanns, P. B. M. W. M. The Discovery of Potent Nonpeptide Angiotensin II Receptor Antagonists: A new Class of Potent Antihypertensives. J. Med. Chem. 1990, 33, 1312.
- (5) Carini, D. J.; Dunica, J. V.; Johnson, A. L.; Chiu, T. A.; Price, W. A.; Wong, P. C.; Timmermanns, P. B. M. W. J. Med. Chem. 1990, 33, 1330.

 Table I. Distances between the Centers of Tetrazole Rings in

 Figure 1 Superpositions

<u> </u>	-				
	compd	distance, Å	compd	distance, Å	
	6a	1.1	6d	2.4	
	6b	3.3	6e	2.0	
	6c	2.8			

structure-activity relationships for this class of compound remain to be fully explored. Starting from the structure of DuP 753, we synthesized a series of more rigid analogues by replacing the biphenyl moiety of DuP 753 by either a naphthalene or a 1,2,3,4-tetrahydronaphthalene ring. The relative positioning of the acidic function and the methyleneimidazole substituent at the naphthalene ring were varied. All compounds were tested for their binding affinity to the AT_1 receptor⁶ in smooth muscle cells from rat aorta. In addition most of the compounds were also evaluated in a functional assay, namely the inhibition of the AII-induced contraction in aortic rings from rabbit. The aim of the study was to get more insight into the steric arrangement of the two pharmacophoric groupssubstituted imidazole and acid function-at the site of the AT_1 receptor.

Molecular Modeling

The objective of this modeling study was first to determine how the naphthalenic derivatives envisaged for synthesis compared with DuP 753 in terms of the relative

⁽⁶⁾ According to Bumpus et al. (Hypertension, in press), the two known AII receptor subtypes are named AT₁ and AT₂. All vascular effects of AII seem to be mediated via the AT₁ receptor subtype. For a characterization of the receptor subtypes, see: Whitebread, S.; Mele, M.; Kamber, B.; de Gasparo, M. Biochem. Biophys. Res. Commun. 1989, 163, 284.



Figure 1. Stereoplot of DuP 753, assumed bioactive conformation.



Figure 2. Naphthalenic derivatives 6a-e (thick line) superimposed on DuP 753 (thin line). Parts of the naphthalenic moieties of these compounds are located in regions of space not occupied by DuP 753. If one classes the molecules according to which region of space their naphthalene ring occupies, three groups can be formed: 6a and 6c, 6b and 6e, and finally 6d.

three-dimensional positioning of the *n*-butylimidazole and the tetrazole pharmacophoric groups. The first step of the study was to derive minimum-energy conformations for DuP 753 and the naphthalenic compounds. For each molecule, starting conformations were generated by using the CONCEPTOR program⁷ and were subsequently minimized in BATCHMIN⁸ employing the NCC force field.⁹ Then, by using the program GRASP,¹⁰ the calculated low-

- (7) CONCEPTOR: in-house molecular modeling program written by N.C. Cohen, similar to SCRIPT: Cohen, N. C.; Colin, P.; Lemoine, G. Tetrahedron 1981, 37, 1711.
- (8) 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.
- (9) For the NCC force field, see: Cohen, N. C. Advances in Drug Research; Testa, B., Eds.; Academic Press: New York, 1985; Vol. 14, p 50 and references therein.
- (10) GRASP: "Graphics Applied to the Superpositioning Problem"; in-house molecular modeling program for the superpositioning of molecules written by J.E. Pearson. A short description is given in the Experimental Section.

energy conformer (energy within 3 kcal/mol of the global minimum) that fits best DuP 753 in terms of *n*-butylimidazole and tetrazole overlap was determined for each of the naphthalenic derivatives. The template conformation used for DuP 753 in these structural comparisons is shown in Figure 1. It is one of the calculated lowest energy conformers presenting a perpendicular arrangement of the imidazole and middle phenyl ring of the molecule. Structure-activity data concerning cyclized analogues prepared in our laboratories (data not shown) suggest that DuP 753 adopts such a conformation at the AT₁ receptor.

The results of this analysis are visualized in Figure 2, where the *n*-butylimidazole moieties of the naphthalenic compounds in their "best fit" conformations have been exactly superimposed on that of the template conformation of DuP 753. In these superpositions, the extent to which the naphthalenic derivatives mimic the spatial arrangement of the imidazole and tetrazole pharmacophore groups of DuP 753 can be estimated by measuring the distance separating the respective tetrazole rings of the superimposed molecules. These distances are reported in Table I. Table II. Naphthalene Derivatives: Receptor Binding Activity and Inhibition of All Induced Contractions in Rabbit Aortic Rings



				• •	п			
compd	R ₁	R ₂	position of tetrazole subst	position of imidazole subst	binding IC ₅₀ ,° µM	rabbit aortic ring IC ₅₀ , ^a µM	mp, °C	anal.
6 a .	Cl	CH ₂ OH	1	5	1.1	0.7	168-170	C, H, Cl, N
6b	Cl	CH ₂ OH	1	7	55	nt ^b	178-179	C, H, Cl, N
6c	Cl	CH ₂ OH	2	5	4.1	2.6	20 9– 211	C, H, Cl, N
6d	Cl	CH ₂ OH	2	6	0.6	1.6	212-214	C, H, Cl, N
6e	Cl	CH ₂ OH	2	7	20	nt	18 9–19 1	C, H, Cl, N
7 DuP 753	CH₂OH	Cl	2	6	0.2 0.026	0.12 0.024	197–1 99	C, H, Cl, N

^a All tests were performed in duplicate. For details see the Experimental Section. ^bNot tested.

On the basis of this analysis and assuming that the chosen template conformation is representative of the conformation DuP 753 adopts when it binds to the AT_1 receptor, the following conclusions could be drawn concerning the naphthalenic structures envisaged for synthesis.

(1) All molecules are able to mimic to a reasonable extent the spatial disposition of the imidazole and tetrazole pharmacophore of DuP 753 (maximum deviation of the tetrazole ring 3.3 Å in structure **6b**).

(2) The most and least promising compounds judging on this sole geometric criterion appear to be 6a (1.1 Å) and 6b (3.3 Å), respectively.

(3) Taking into consideration that new regions of the AT_1 receptor are explored by the naphthalenic derivatives compared to DuP 753, the former molecules can be sorted in three groups, comprising respectively 6a and 6c, 6b and 6e, and 6d (see Figure 2). Compounds belonging to the same group occupy approximately the same volume of space, except for the tetrazole functions, in their presumed active conformation. Predictions of relative activities based on the above analysis have therefore a firmer ground if one compares molecules of the same class. Along this line, 6a was predicted to be more active than 6c, and 6e more active than 6b.

In a second part of the modeling study a tetrahydro version of the naphthalene derivative 6d (7) (most active derivatives in the naphthalene series) was again compared with DuP 753. It was found that an additional substituent in the α -position to the acidic function would help this function to adopt an axial orientation at the saturated ring, allowing a better overlap of the pharmacophores with DuP 753 (see Figure 3). On this basis an activity increase was expected for 23a and 23b compared to 13a and 13b.

Chemistry

Starting from the known cyanomethylnaphthalene isomers $1a-e^{11-13}$ the naphthalene derivatives described in Table II were prepared by standard chemical procedures (Scheme I). The reaction of the bromomethyl compounds 2a-e with imidazole 3^2 using sodium hydride as a base invariably produced a ca. 1:1 mixture of the two regioisomers, which however could be readily separated by flash chromatography. On TLC, the faster moving compound always corresponded to the 4-chloro-5-(hydroxymethyl)



Figure 3. Stereoplot of low-energy conformation of 23a (thick line) that fits best the assumed active conformation of DuP 753 (thin line).



isomer (assignment based on proton NMR). The 2,6substituted tetrahydronaphthalene derivatives (Table II)

⁽¹¹⁾ Yoshida, K.; Nagase, S. J. Am. Chem. Soc. 1979, 101 (15), 4268.

 ⁽¹²⁾ Gore, P. H.; Siddiquer, A. S.; Thorburn, S. J. Chem. Soc. 1972,
 (2), 1781.

⁽¹³⁾ Takiura, J. Pharm. Soc. Jpn. 1943, 63, 40, 45; Chem. Abstr. 1950, 7280.

Scheme II





 $R_1 = CI; R_2 = CH_2OH$ $R_1 = CH_2OH; R_2 = CI$

were obtained via a Birch reduction of the known hydroxymethyl ester 8^{14} (Scheme II). The double bond in position 3,4 was reduced very cleanly by using the sodium borohydride-cobalt chloride complex. Direct conversion of the resulting benzylic alcohol 10 with trimethylbromosilane in chloroform led to bromide 11, which was again reacted with imidazole 3. The two regioisomeric esters 12a and 12b were subsequently hydrolyzed to acids 13a and 13b. For the preparation of tetrazoles 18a and 18b, an intermediate protection of the benzylic hydroxyl group in the intermediate 10 was necessary. Interestingly, methyl ether 15 could afterwards be directly transformed with trimethyliodosilane to iodide 16. All attempts to methylate a protected derivative of 10 in the α -position of the carboxylic ester group failed. Therefore an alternative route to prepare the desired 2-methyl derivatives 23 was attempted (Scheme III). Trapping of the Birch reaction product with an excess of methyl iodide, as described by Basu and Mukherjee,¹⁶ gave the doubly methylated product 20 in good yield. Subsequent alkylation with

⁽¹⁵⁾ A different route to the ethyl ester derivative was described: Kanao, M.; Watanabe, Y.; Kimura, Y.; Saegusa, J.; Yamamoto, K.; Kanno, H.; Kanaya, N.; Kubo, H.; Ashida, S.; Ishikawa, F. J. Med. Chem. 1989, 32 (12), 1326.

⁽¹⁴⁾ Dawson, M. I.; Chan, R. L. S. U.S. Patent 4 456 618, 1982.

⁽¹⁶⁾ Basu, B.; Mukherjee, D. J. Chem. Soc. Chem. Commun. 1984, 105.

Table III. Tetrahydronaphthalene Derivatives: Receptor Binding Activity and Inhibition of All Induced Contractions in Rabbit Aortic Rings



	→ → H ₄							
compd	R ₁	R ₂	R ₃	R4	binding IC ₅₀ ,° µM	rabbit aortic ring IC ₅₀ , ^a µM	mp, °C	anal.
13a	Cl	CH ₂ OH	COOH	н	8.9	1.2	175-177	C, H, Cl, N
13b	CH.OH	Cl	COOH	н	1.1	0.3	212-214	C, H, Cl, N
18a	Cl	CH.OH	2-tetrazolyl	н	5.4	1.9	193194	C, H, Cl, N
18b	CH.OH	Cl	2-tetrazolvl	н	1.4	0.56	166-168	C, H, Cl, N
23a	Cl	CH ₂ OH	COOH	CH ₃	4.6	2.2	169-170	C, H, Cl, N
23b	CH.OH	Cl	COOH	CH	2.8	2.7	205-206	C, H, Cl, N
DuP 753	2			<u>j</u>	0.026	0.024		

^a All tests were performed in duplicate. For details see the Experimental Section.

Scheme III OCH₃ 1. NH₃/Na 2. CH3 CH3 соосн, COOCH₃ 19 NaBH₄ CoCl₂ осн₃ TMS СН₃ СН₃ соосн3 COOCH₃ 20 21 NaH NaOH СН₃ CH₃ соосн3 соон 22 a $R_1 = CI; R_2 = CH_2OH$ 23 a 22 b R1 = CH2OH; R2 = CI

imidazole 3 and ester hydrolysis led to the desired products 23a and 23b.

Discussion

With one exception (compound 13a), receptor binding activity determined in rat aortic smooth muscle cell preparation and functional activity determined in the rabbit thoracic aortic ring are in relative good agreement, indicating that the angiotensin II induced contraction in rabbit aorta is mediated via the same receptor as found in rat vascular smooth muscle $(AT_1, \text{ see ref } 17)$.

 $R_1 = CI; R_2 = CH_2OH$ 23 b $R_1 = CH_2OH; R_2 = CI$

Compared to the standard compound DuP 753, all naphthalene and tetrahydronaphthalene derivatives showed weaker potency in receptor binding and also in the functional test. This may either be due to the increased rigidity of the spacer, which does not allow slight conformational adjustments needed for an optimal receptor fit, or it could reflect the fact that the biphenyl moiety of DuP 753 itself may contribute to receptor binding in a specific manner.

In the naphthalene series, the molecular modeling study based only on geometric criteria correctly predicted that

 ⁽¹⁷⁾ Criscione, L.; Thomann, H.; Whitebread, St.; de Gasparo, M.;
 Bühlmayer, P.; Herold, P.; Ostermayer, F.; Kamber, B. J. Card, Pharmacol. 1990, 16 (Suppl. 4), 56.

De Lean, A.; Munson, P. J.; Rodbard, D. Am. J. Physiol. 1978, (18) E97-E111, 235.

6a should be more active than 6c, and 6e more active than 6b. In fact 6b was the least active compound of the series and 6a and 6d were the best binders among the derivatives with the 4-chloro-5-(hydroxymethyl) substitution pattern at the imidazole ring. Surprisingly and in contrast to the observation with the DuP 753 isomers,³ 4-(hydroxymethyl)-5-chloroimidazole isomer 7 was found to be more active than its analogue 6d by a factor of 3 in binding and even by a factor of more than 10 in the functional test. The same observation was also made in the tetrahydronaphthalene series, where the 4-(hydroxymethyl)-5-chloro isomers consistently showed greater potency than the corresponding 4-chloro-5-(hydroxymethyl) analogues. This may indicate that the imidazole pharmacophore in these series does not bind in exactly the same manner to the AT_1 receptor as DuP 753.

Overall the 2,6-substituted tetrahydronaphthalene derivatives showed slightly weaker potency than the corresponding 2,6-substituted naphthalene derivatives 6d and 7. In contrast to our expectation based on a conformational argument, the additional methyl group in the α position to the carboxylic acid group (compounds 23a,b) did not lead to a substantial potency increase. Whether this is due to detrimental steric hindrance or unfavorable electronic effects remains unclear. Replacement of the carboxylic acid group by a tetrazole, which in the case of DuP 753 increased potency by a factor of 10 (ref 3), also had no beneficial effect here. An overlap of carboxylic acid 13a and tetrazole 18a demonstrated, however, that the positions of the acidic functions in these two molecules are very close. On this basis a similar receptor binding affinity is therefore not unexpected.

Experimental Section

Chemistry. Thin-layer chromatography (TLC) was performed on silica gel plates (E. Merck, silica gel 60 F-254), and components were visualized by UV254 or CPS spray (phosphomolybdic acid/cerium(IV) sulfate/ H_2SO_4/H_2O). Where R_f values are given the solvent system used was always ethyl acetate/hexane 2:1. Column flash chromatography was performed on silica gel 60, 0.04-0.063 mm (E. Merck), eluting under a positive pressure of ca. 20 psi of nitrogen ensuring a flow rate of ca. 5 mL/min. NMR spectra were recorded on a Bruker AM-360 spectrometer or a Varian Gemini 200/300 and are expressed in parts per million (ppm) from tetramethylsilane as internal standard. All compounds have NMR spectra consistent with the assigned structure. Regular mass spectra were obtained with a Varian CH7/MAT212. FAB MS were recorded on a V6 Analytical ZAB-HF spectrometer. Melting points were determined on a melting point apparatus (Büchi 520) and are uncorrected. Analytical samples were dried in vacuo and were free of significant impurities on TLC. Where analyses are indicated for C, H, N, and halogen, analytical values are within $\simeq 0.4\%$ of calculated values.

1-Cyano-5-(bromomethyl)naphthalene (2a). A solution of $1a^{11}$ (2.96 g, 17.7 mmol), N-bromosuccinimide (3.15 g, 17.7 mmol, 1.0 equiv), azaisobutyronitrile (0.10 g, 0.61 mmol, 0.034 equiv), and benzoyl peroxide (0.05 g, 0.17 mmol, 0.01 equiv), in 300 mL of carbon tetrachloride was refluxed for 1 h. After cooling to room temperature, the resulting suspension was filtered and the filtrate concentrated in vacuo. Flash chromatography of the remaining residue in 1:1 dichloromethane/hexane gave after recrystallization from ethyl acetate/hexane 2.31 g (53%) of pure 2a: mp 135–136 °C; NMR (DMSO- d_g) δ 8.58 (1 H, d, J = 9 Hz), 8.15 (1 H, d, J = 9 Hz), 7.92–7.75 (3 H, m), 5.28 (2 H, s). Anal. (C₁₂H₈BrN) C, H, Br, N.

The following were analogously prepared.

1-Cyano-7-(bromomethyl)naphthalene (2b) was prepared from $1b^{12}$ (6.0 g, 35.9 mmol) to give 5.87 g (66%) of 2b: mp 95–97 °C; NMR (DMSO- d_6) δ 8.33–8.12 (4 H, m), 7.80–7.67 (2 H, m), 5.01 (2 H, s). Anal. (C₁₂H₈BrN) C, H, Br, N.

2-Cyano-5-(bromomethyl)naphthalene (2c) was prepared from 1c¹³ (3.34 g, 20 mmol) to give 3.63 g (74%) of 2c: mp 127-128 °C; NMR (DMSO- d_6) δ 8.66 (1 H, d, J = 1 Hz), 8.37 (1 H, d, J = 9 Hz), 8.10 (1 H, d, J = 9 Hz), 7.98–7.61 (3 H, m), 5.25 (2 H, s). Anal. ($C_{12}H_8BrN$) C, H, Br, N.

2-Cyano-6-(bromomethyl)naphthalene (2d) was prepared from $1d^{12}$ (13.4 g, 80 mmol) to give 12.5 g (64%) of 2d: mp 138–139 °C; NMR (DMSO- d_6) δ 8.58 (1 H, s), 8.13 (1 H, s), 8.13–8.05 (2 H, m), 7.83 (1 H, dd, J = 1/9 Hz), 7.73 (1 H, dd, J = 1/9 Hz), 4.90 (2 H, s). Anal. (C₁₂H₈BrN) C, H, Br, N.

2-Cyano-7-(bromomethyl)naphthalene (2e) was prepared from $1e^{12}$ (6.93 g, 41.5 mmol) to give 7.24 g (71%) of 2e: mp 125-126 °C; NMR (DMSO- d_6) δ 8.58 (1 H, s), 8.13 (1 H, s), 8.13-8.05 (2 H, m), 7.85-7.75 (2 H, m), 4.92 (2 H, m). Anal. (C₁₂H_BBrN) C, H, Br, N.

2-n-Butyl-4-chloro-5-(hydroxymethyl)-1-[(1-cyanonaphthalen-5-yl)methyl]imidazole (4a) and Its Regioisomer 5a. To a suspension of sodium hydride (55%, 0.218 g, 5.0 mmol, 1.0 equiv) in 10 mL of dimethylformamide at 25 °C was added dropwise a solution of 2-n-butyl-4(5)-chloro-5(4)-(hydroxymethyl)imidazole³ (0.943 g, 5.0 mmol, 1.0 equiv) in 5 mL of dimethylformamide. The resulting mixture was stirred at 25 °C for 1 h, and then to this mixture was added dropwise a solution of 2a (1.23 g, 5.0 mmol) in 5 mL of dimethylformamide. Finally, the reaction mixture was stirred for 1 h at room temperature. The solvent was removed in vacuo and the residue was dissolved in ethyl acetate. After extraction with water and brine, the organic layer was dried (MgSO₄) and the solvent was removed in vacuo. The residue was flash chromatographed over silica gel (elution: ethyl acetate/hexane 2:1), affording after recrystallization from ethyl acetate/hexane 0.76 g (43%) of pure 4a, the regioisomer with the higher R_i (0.23), and 0.37 g (21%) of pure 5a the regioisomer with the lower R_{f} (0.04).

4a: mp 185–186 °C; NMR (DMSO- d_6) δ 8.56 (1 H, d, J = 9 Hz), 8.28 (1 H, d, J = 9 Hz), 8.08 (1 H, d, J = 9 Hz), 7.83 (1 H, dd, J = 9/9 Hz), 7.72 (1 H, dd, J = 9/9 Hz), 6.61 (1 H, d, J = 9 Hz), 5.83 (2 H, s), 5.17 (1 H, t, J = 6 Hz), 4.27 (2 H, d, J = 6 Hz), 2.45 (2 H, t, J = 7 Hz), 1.48 (2 H, m), 1.18 (2 H, m), 0.74 (3 H, t, J = 7 Hz). Anal. ($C_{20}H_{20}CIN_3O$) C, H, Cl, N.

5a: mp 221–222 °C; NMR (DMSO- d_6) δ 8.54 (1 H, d, J = 9 Hz), 8.28 (1 H, d, J = 9 Hz), 8.08 (1 H, d, J = 9 Hz), 7.83 (1 H, dd, J = 9/9 Hz), 7.72 (1 H, dd, J = 9/9 Hz), 6.57 (1 H, d, J = 9 Hz), 5.77 (2 H, s), 4.98 (1 H, t, J = 6 Hz), 4.34 (2 H, d, J = 6 Hz), 2.55 (2 H, t, J = 7 Hz), 1.53 (2 H, m), 1.23 (2 H, m), 0.77 (3 H, t, J = 7 Hz). Anal. (C₂₀H₂₀ClN₃O) C, H, Cl, N.

The following were analogously prepared.

2-*n*-Butyl-4-chloro-5-(hydroxymethyl)-1-[(1-cyanonaphthalen-7-yl)methyl]imidazole (4b) and its regioisomer 5b were prepared from 2b (2.46 g, 10 mmol) to afford after recrystallization from ethyl acetate/hexane 1.58 g (45%) of pure 4b (R_f 0.31) and 0.74 g (21%) of pure 5b (R_f 0.06).

4b: mp 137-139 °C; NMR (DMSO- d_6) δ 8.32 (1 H, d, J = 9 Hz), 8.18 (1 H, d, J = 9 Hz), 8.12 (1 H, d, J = 9 Hz), 7.82 (1 H, s), 7.68 (1 H, dd, J = 9/9 Hz), 7.43 (1 H, d, J = 9 Hz), 5.53 (2 H, s), 5.27 (1 H, t, J = 6 Hz), 4.37 (2 H, d, J = 6 Hz), 2.53 (2 H, t, J = 7 Hz), 1.42 (2 H, m), 1.21 (2 H, m), 0.68 (3 H, t, J = 7 Hz). Anal. (C₂₀H₂₀ClN₃O) C, H, Cl, N.

5b: mp 188–189 °C; NMR (DMSO- d_6) δ 8.32 (1 H, d, J = 9 Hz), 8.19 (1 H, d, J = 9 Hz), 8.15 (1 H, d, J = 9 Hz), 7.84 (1 H, s), 7.68 (1 H, dd, J = 9/9 Hz), 7.38 (1 H, d, J = 9 Hz), 5.48 (2 H, s), 4.93 (1 H, t, J = 6 Hz), 4.30 (2 H, d, J = 6 Hz), 2.63 (2 H, t, J = 7 Hz), 1.49 (2 H, m), 1.27 (2 H, m), 0.76 (3 H, t, J = 7 Hz). Anal. (C₂₀H₂₀ClN₃O) C, H, Cl, N.

2-*n*-Butyl-4-chloro-5-(hydroxymethyl)-1-[(2-cyanonaphthalen-5-yl)methyl]imidazole (4c) and its regioisomer 5c were prepared from 2c (1.23 g, 5.0 mmol) to afford after recrystallization from ethyl acetate/hexane 1.07 g (60%) of pure 4c (R_f 0.33) and 0.44 g (25%) of pure 5c (R_f 0.05).

4c: mp 115–116 °C; NMR (DMSO- d_{e}) & 8.68 (1 H, s), 8.35 (1 H, d, J = 9 Hz), 8.02 (1 H, d, J = 9 Hz), 7.96 (1 H, d, J = 9 Hz), 7.59 (1 H, dd, J = 9/9 Hz), 6.63 (1 H, d, J = 9 Hz), 5.80 (2 H, s), 5.17 (1 H, t, J = 6 Hz), 4.27 (2 H, d, J = 6 Hz), 2.46 (2 H, t, J = 7 Hz), 1.48 (2 H, m), 1.20 (2 H, m), 0.73 (3 H, t, J = 7 Hz). Anal. (C₂₀H₂₀ClN₃O) C, H, Cl, N.

5c: mp 179–180 °C; NMR (DMSO- d_{g}) δ 8.68 (1 H, s), 8.41 (1 H, d, J = 9 Hz), 8.03 (1 H, d, J = 9 Hz), 7.97 (1 H, d, J = 9 Hz), 7.60 (1 H, dd, J = 9/9 Hz), 6.57 (1 H, d, J = 9 Hz), 5.73 (2 H, s), 4.97 (1 H, t, J = 6 Hz), 4.35 (2 H, d, J = 6 Hz), 2.55 (2 H, t, J = 7 Hz), 1.53 (2 H, m), 1.24 (2 H, m), 0.74 (3 H, t, J = 7 Hz).

Nonpeptidic Angiotensin II Antagonists

Anal. $(C_{20}H_{20}ClN_{3}O)$ C, H, Cl, N.

2-*n*-Butyl-4-chloro-5-(hydroxymethyl)-1-[(2-cyanonaphthalen-6-yl)methyl]imidazole (4d) and its regioisomer 5d were prepared from 2d (1.23 g, 5.0 mmol) to afford after recrystallization from ethyl acetate/hexane 0.93 g (53%) of pure 4d (R_f 0.25) and 0.33 g (19%) of pure 5d (R_f 0.04).

4d $(R_f 0.25)$ and 0.33 g (19%) of pure 5d $(R_f 0.04)$. 4d: mp 178–179 °C; NMR (DMSO- d_6) δ 8.57 (1 H, s), 8.08 (2 H, d, J = 9 Hz), 7.78 (1 H, d, J = 9 Hz), 7.63 (1 H, s), 7.46 (1 H, d, J = 9 Hz), 5.47 (2 H, s), 5.25 (1 H, t, J = 6 Hz), 4.37 (2 H, d, J = 6 Hz), 2.50 (2 H, t, J = 7 Hz), 1.43 (2 H, m), 1.21 (2 H, m), 0.72 (3 H, t, J = 7 Hz). Anal. (C₂₀H₂₀ClN₃O) C, H, Cl, N.

5d: mp 144-145 °C; NMR (DMSO- d_8) & 8.58 (1 H, s), 8.08 (2 H, dd, J = 9/9 Hz), 7.78 (1 H, d, J = 9 Hz), 7.62 (1 H, s), 7.41 (1 H, d, J = 9 Hz), 5.40 (2 H, s), 4.92 (1 H, t, J = 6 Hz), 4.32 (2 H, d, J = 6 Hz), 2.62 (2 H, t, J = 7 Hz), 1.53 (2 H, m), 1.27 (2 H, m), 0.77 (3 H, t, J = 7 Hz). Anal. (C₂₀H₂₀ClN₃O) C, H, Cl, N.

2-*n*-Butyl-4-chloro-5-(hydroxymethyl)-1-[(2-cyanonaphthalen-7-yl)methyl]imidazole (4e) and its regioisomer 5e were prepared from 2e (1.23 g, 5.0 mmol) to afford after recrystallization from ethyl acetate/hexane 0.88 g (50%) of pure 4e (R_f 0.26) and 0.66 g (37%) of pure 5e (R_f 0.05).

4e: mp 110–111 °C; NMR (DMSO- $d_{\rm e}$) & $\dot{\rm s}$ $\dot{\rm s}$.56 (1 H, s), 8.10 (1 H, d, J = 9 Hz), 8.05 (1 H, d, J = 9 Hz), 7.77 (1 H, d, J = 9 Hz), 7.67 (1 H, s), 7.48 (1 H, d, J = 9 Hz), 5.45 (2 H, s), 5.23 (1 H, t, J = 6 Hz), 4.36 (2 H, d, J = 6 Hz), 2.48 (2 H, t, J = 7 Hz), 1.43 (2 H, m), 1.21 (2 H, m), 0.73 (3 H, t, J = 7 Hz). Anal. (C₂₀-H₂₀ClN₃O) C, H, Cl, N.

5e: mp 131–132 °C; NMR (DMSO- d_0) δ 8.57 (1 H, s), 8.11 (1 H, d, J = 9 Hz), 8.06 (1 H, d, J = 9 Hz), 7.79 (1 H, d, J = 9 Hz), 7.66 (1 H, s), 7.45 (1 H, d, J = 9 Hz), 5.38 (2 H, s), 4.91 (1 H, t, J = 6 Hz), 4.30 (2 H, d, J = 6 Hz), 2.60 (2 H, t, J = 7 Hz), 1.52 (2 H, m), 1.25 (2 H, m), 0.77 (3 H, t, J = 7 Hz). Anal. (C₂₀-H₂₀ClN₃O) C, H, Cl, N.

2-n-Butyl-4-chloro-5-(hydroxymethyl)-1-[[1-(1H-tetrazol-5-yl)naphthalen-5-yl]methyl]imidazole (6a). 2-n-Butyl-4-chloro-5-(hydroxymethyl)-1-[(1-cyanonaphthalen-5-yl)methyl]imidazole (4a) (0.70 g, 1.98 mmol), tributyltin azide (1.31 g, 3.96 mmol, 2 equiv), and xylene (20 mL) were mixed and refluxed for 18 h. The solvent was removed in vacuo and the residue was stirred with 1 N NaOH (50 mL) for 0.5 h. The aqueous mixture was extracted with diethyl ether $(3 \times 50 \text{ mL})$. After separation the aqueous phase was acidified with 4 N HCl to pH 3. The solid which precipitated was collected and gave after recrystallization from 2-propanol/ethyl acetate 0.31 g (40%) of pure 6a: mp 168–170 °C; NMR (DMSO- d_6) δ 8.43 (1 H, d, J = 9 Hz), 8.39 (1 H, d, J = 9 Hz), 8.03 (1 H, d, J = 9 Hz), 7.84 (1 H, t, J = 9 Hz), 7.55 (1 H, t, J = 9 Hz), 6.51 (1 H, d, J = 9 Hz), 5.85 (2 H, s), 5.30-5.10 (1 H, m), 4.27 (2 H, s), 2.48 (2 H, t, J = 7 Hz), 1.50 (2 H, m), 1.20 (2 H, m), 0.74 (3 H, t, J = 7 Hz). Anal. $(C_{20}H_{21}ClN_6O)$ C, H, Cl, N.

The following were analogously prepared.

2-*n***-Butyl-4-chloro-5-(hydroxymethyl)-1-[[1-(1***H***-tetrazol-5-yl)naphthalen-7-yl]methyl]imidazole (6b) was prepared from 4b (0.708 g, 2.0 mmol) to give after recrystallization from 2-propanol/ethyl acetate 0.14 g (18%) of pure 6b: mp 178–179 °C; NMR (DMSO-d_6) & 8.38 (1 H, s), 8.16 (1 H, d, J = 9 Hz), 8.05 (1 H, d, J = 9 Hz), 7.98 (1 H, d, J = 9 Hz), 7.70 (1 H, t, J = 9 Hz), 7.30 (1 H, d, J = 9 Hz), 5.45 (2 H, s), 5.45–5.00 (1 H, m), 4.35 (2 H, s), 2.50 (2 H, t, J = 7 Hz), 1.38 (2 H, m), 1.15 (2 H, m), 0.67 (3 H, t, J = 7 Hz). Anal. (C₂₀H₂₁ClN₆O) C, H, Cl, N.**

2-*n***-Butyl-4-chloro-5-(hydroxymethyl)-1-[[2-(1***H***-tetrazol-5-yl)naphthalen-5-yl]methyl]imidazole (6c) was prepared from 4c (0.708 g, 2.0 mmol) to give after recrystallization from 2-propanol/ethyl acetate 0.39 g (49%) of pure 6c: mp 209-211 °C; NMR (DMSO-d_0 \delta 8.72 (1 H, s), 8.40 (1 H; d, J = 9 Hz), 8.23 (1 H, d, J = 9 Hz), 8.03 (1 H, d, J = 9 Hz), 7.53 (1 H, t, J = 9 Hz), 6.54 (1 H, d, J = 9 Hz), 5.82 (2 H, s), 5.30-5.10 (1 H, m), 4.27 (2 H, s), 2.48 (2 H, t, J = 7 Hz), 1.49 (2 H, m), 1.18 (2 H, m), 0.73 (3 H, t, J = 7 Hz). Anal. (C₂₀H₂, ClN₂₀O) C, H, Cl, N.**

(3 H, t, J = 7 Hz). Anal. (C₂₀H₂₁ClN₆O) C, H, Cl, N. 2-n-Butyl-4-chloro-5-(hydroxymethyl)-1-[[2-(1*H*-tetrazol-5-yl)naphthalen-6-yl]methyl]imidazole (6d) was prepared from 4d (0.874 g, 2.47 mmol) to give after recrystallization from 2-propanol/ethyl acetate 0.51 g (52%) of pure 6d: mp 212-214 °C; NMR (DMSO-d₆) δ 8.64 (1 H, s), 8.09 (3 H, m), 7.61 (1 H, s), 7.41 (1 H, d, J = 9 Hz), 5.45 (2 H, s), 5.35-5.15 (1 H, m), 4.37 (2 H, s), 2.50 (2 H, t, J = 7 Hz), 1.43 (2 H, m), 1.19 (2 H, m), 0.70 (3 H, t, J = 7 Hz). Anal. $(C_{20}H_{21}ClN_6O) C, H, Cl, N.$

2-n-Butyl-4-chloro-5-(hydroxymethyl)-1-[[2-(1*H*-tetrazol-5-yl)naphthalen-7-yl]methyl]imidazole (6e) was prepared from 4e (0.86 g, 2.43 mmol) to give after recrystallization from 2-propanol/ethyl acetate 0.45 g (47%) of pure 6e: mp 189–191 °C; NMR (DMSO- d_6) δ 8.59 (1 H, s), 8.11 (2 H, m), 8.02 (1 H, d, J = 9 Hz), 7.60 (1 H, s), 7.45 (1 H, d, J = 9 Hz), 5.46 (2 H, s), 5.33–5.20 (1 H, m), 4.37 (2 H, s), 2.50 (2 H, t, J = 7 Hz), 1.44 (2 H, m), 1.21 (2 H, m), 0.70 (3 H, t, J = 7 Hz). Anal. (C₂₀H₂₁ClN₆O) C, H, Cl, N.

2-*n*-Butyl-5-chloro-4-(hydroxymethyl)-1-[[2-(1*H*-tetrazol-5-yl)naphthalen-6-yl]methyl]imidazole (7) was prepared from 5d (0.28 g, 0.79 mmol) to give after recrystallization from 2-propanol 0.18 g (57%) of pure 7: mp 188-190 °C; NMR (DMSO- d_6) δ 8.64 (1 H, s), 8.10 (3 H, m), 7.58 (1 H, s), 7.35 (1 H, d, J = 9 Hz), 5.40 (2 H, s), 5.15-4.75 (1 H, m), 4.31 (2 H, s), 2.63 (2 H, t, J = 7 Hz), 1.52 (2 H, m), 1.25 (2 H, m), 0.76 (3 H, t, J = 7 Hz). Anal. (C₂₀H₂₁ClN₆O) C, H, Cl, N.

2-(Methoxycarbonyl)-6-(hydroxymethyl)-1,2-dihydronaphthalene (9). Small sodium pieces (4.26 g, 0.185 mol, 5 equiv) were dissolved in liquid ammonia (400 mL) at -60 °C. After 2 min, a solution of 8¹⁴ (8.0 g, 0.037 mol) in anhydrous tetrahydrofuran (80 mL) was added dropwise at -70 to -65 °C (3 min). The reaction mixture was stirred at -70 °C for 1 h. Thereafter an aqueous ammonium chloride solution (100 mL) was added to quench excess sodium amide. Ammonia was allowed to evaporate at 0 °C. The residue was dissolved in water (1 L) and extracted with diethyl ether $(3 \times 600 \text{ mL})$. The organic phases were washed with water and brine and dried $(MgSO_4)$, and the solvent was removed in vacuo. Flash chromatography of the remaining residue in 1:2 ethyl acetate/hexane gave 3.96 g (49%) of pure 9 as an oil: NMR (DMSO- d_6) δ 7.18–7.04 (3 H, m), 6.58 (1 H, dd, J = 2.5/10Hz), 6.05 (1 H, dd, J = 5/10 Hz), 5.11 (1 H, t, J = 6 Hz), 4.45 (2 H, d, J = 6 Hz), 3.64 (3 H, s), 3.58-3.45 (1 H, m), 2.98 (2 H, m)m)

2-(Methoxycarbonyl)-6-(hydroxymethyl)-1,2,3,4-tetrahydronaphthalene (10).¹⁵ To a solution of 9 (3.95 g, 18.1 mmol) and cobalt(II) chloride hexahydrate (4.31 g, 18.1 mmol, 1 equiv) in ethanol (200 mL) under Ar at 0 °C was added sodium borohydride (2.74 g, 72.4 mmol, 4 equiv) in portions. The solution became immediately dark and hydrogen evolved. The mixture was allowed to reach room temperature and was stirred for an additional 30 min. After removal of the solvent, the residue was poured into a mixture of ice/2 N HCl (1:1, 500 mL). The aqueous solution was extracted with dichloromethane $(2 \times 500 \text{ mL})$. The organic layer was dried (MgSO₄), and the solvent was removed in vacuo. Flash chromatography of the remaining residue in 2:1 dichloromethane/diethyl ether gave 3.72 g (93%) of pure 10 as a light solid: mp 76-77 °C; NMR (DMSO-d_g) δ 7.08-7.00 (3 H, m), 5.05 (1 H, t, J = 6 Hz), 4.41 (2 H, d, J = 6 Hz), 3.64 (3 H, s), 3.04–2.68 (5 H, m), 2.23–2.00 (1 H, m), 1.85–1.65 (1 H, m); MS m/e 220.

2-(Methoxycarbonyl)-6-(bromomethyl)-1,2,3,4-tetrahydronaphthalene (11). To a solution of 10 (0.44 g, 2.0 mmol) in chloroform (5 mL) was added trimethylbromosilane (0.46 g, 3.0 mmol, 1.5 equiv). The reaction mixture was stirred at room temperature for 4 h and then diluted with dichloromethane (100 mL) and washed with water (100 mL) and brine (100 mL). The organic phase was dried (MgSO₄), and the solvent was removed in vacuo. Flash chromatography of the remaining residue in dichloromethane gave 0.53 g (93%) of pure 11 as a light yellow oil: NMR (DMSO-d₆) δ 7.32-7.08 (3 H, m), 4.63 (2 H, s), 3.65 (3 H, s), 3.09-2.72 (5 H, m), 2.19-2.03 (1 H, m), 1.85-1.68 (1 H, m); MS m/e 283.

2-*n*-Butyl-4-chloro-5-(hydroxymethyl)-1-[[2-(methoxycarbonyl)-1,2,3,4-tetrahydronaphthalen-6-yl]methyl]imidazole (12a) and Its Regioisomer 12b. To a suspension of sodium hydride (55%, 0.08 g, 1.83 mmol, 1.0 equiv) in dimethylformamide (4 mL) at 25 °C was added dropwise a solution of 2-*n*-butyl-4(5)-chloro-5(4)-(hydroxymethyl)imidazol⁸ (0.345 g, 1.83 mmol, 1.0 equiv) in dimethylformamide (4 mL). The resulting mixture was stirred at 25 °C for 1.5 h. To this mixture was added dropwise a solution of 11 (0.518 g, 1.83 mmol) in dimethylformamide (4 mL). Finally, the reaction mixture was stirred for 2 h at room temperature. The solvent was removed in vacuo; the residue was poured into a mixture of ice/H₂O. The slurry was extracted with ethyl acetate (2 × 100 mL), and the combined extracts were washed with water and brine. The organic phase was dried (MgSO₄) and the solvent was removed in vacuo. Flash chromatography of the residue over silica gel (elution: ethyl acetate/hexane 2:1), afforded 0.39 g (55%) of 12a as a light yellow oil (R_f 0.56 in CH₂Cl₂/MeOH 9:1) and 0.25 g (35%) of 12b as a light yellow oil (R_f 0.46 in CH₂Cl₂/MeOH 9:1).

12a: NMR (DMSO- d_6) δ 7.08 (1 H, d, J = 9 Hz), 6.80 (1 H, s), 6.75 (1 H, d, J = 9 Hz), 5.20 (1 H, t, J = 6 Hz), 5.15 (2 H, s), 4.31 (2 H, d, J = 6 Hz), 3.63 (3 H, s), 3.00–2.65 (5 H, m), 2.47 (2 H, t, J = 7 Hz), 2.13–2.02 (1 H, m), 1.78–1.63 (1 H, m), 1.45 (2 H, m), 1.23 (2 H, m), 0.80 (3 H, t, J = 7 Hz).

12b: NMR (DMSO- d_{6}) δ 7.08 (1 H, d, J = 9 Hz), 6.80 (1 H, s), 6.75 (1 H, d, J = 9 Hz), 5.09 (2 H, s), 4.88 (1 H, t, J = 6 Hz), 4.28 (2 H, d, J = 6 Hz), 3.63 (3 H, s), 3.00–2.62 (5 H, m), 2.56 (2 H, t, J = 7 Hz), 2.13–2.02 (1 H, m), 1.82–1.63 (1 H, m), 1.55 (2 H, m), 1.30 (2 H, m), 0.83 (3 H, t, J = 7 Hz).

2-*n*-Butyl-4-chloro-5-(hydroxymethyl)-1-[(2-carboxy-1,2,3,4-tetrahydronaphthalen-6-yl)methyl]imidazole (13a). A mixture of 12a (0.39 g, 1.0 mmol), methyl alcohol (10 mL), water (4 mL), and 2 N NaOH (1.0 mL, 2 mmol, 2 equiv) was stirred at room temperature overnight. A 1.0-mL portion of 2 N HCl was added, and the methyl alcohol was removed in vacuo. The residue was extracted with ethyl acetate (2 × 20 mL). The organic phases were washed with water and brine, dried (MgSO₄), and then concentrated at reduced pressure. Filtration of the crystals and recrystallization from ethyl acetate yielded 218 mg (58%) of pure 13a: mp 175-177 °C; NMR (DMSO-d₆) δ 12.30 (1 H, br s), 7.07 (1 H, d, J = 9 Hz), 6.80 (1 H, s), 6.75 (1 H, d, J = 9 Hz), 5.27-5.08 (3 H, m), 4.30 (2 H, s), 2.97-2.56 (5 H, m), 2.47 (2 H, t, J = 7 Hz), 2.12-2.00 (1 H, m), 1.78-1.62 (1 H, m), 1.47 (2 H, m), 1.23 (2 H, m), 0.80 (3 H, t, J = 7 Hz). Anal. (C₂₀H₂₅ClN₂O₃) C, H, Cl, N.

2-*n*-Butyl-5-chloro-4-(hydroxymethyl)-1-[(2-carboxy-1,2,3,4-tetrahydronaphthalen-6-yl)methyl]imidazole (13b). A mixture of 12b (0.25 g, 0.64 mmol), methyl alcohol (10 mL), water (4 mL), and 2 N NaOH (1.0 mL, 2 mmol, 3.125 equiv) was stirred at room temperature overnight. A 1.0-mL portion of 2 N HCl was added, and the resulting precipitate was filtered and washed with water and ethyl acetate. The solid was dried at 80 °C under high vacuum overnight to yield 145 mg (60%) of pure 13b: mp 212-214 °C; NMR (DMSO- d_6) δ 12.35 (1 H, br s), 7.08 (1 H, d, J = 9 Hz), 6.79 (1 H, s), 6.73 (1 H, d, J = 9 Hz), 5.08 (2 H, s), 4.88 (1 H, t, J = 6 Hz), 4.28 (2 H, d, J = 6 Hz), 2.96-2.58 (5 H, m), 2.55 (2 H, t, J = 7 Hz), 2.12-2.00 (1 H, m), 1.78-1.62 (1 H, m), 1.53 (2 H, m), 1.29 (2 H, m), 0.83 (3 H, t, J = 7 Hz). Anal. (C₂₀H₂₅ClN₂O₃) C, H, Cl, N.

2-(Methoxycarbonyl)-6-(methoxymethyl)-1,2,3,4-tetrahydronaphthalene (14). To a solution of 10 (3.72 g, 16.9 mmol) in chloroform (60 mL) was added at room temperature silver(I) oxide (15.7 g, 67.6 mmol, 4 equiv) and iodomethane (8.41 mL, 135.2 mmol, 8 equiv). The reaction mixture was stirred at 50 °C overnight. After cooling to room temperature, the slurry was filtered and the solvent from the filtrate was removed in vacuo. Flash chromatography of the remaining residue in dichloromethane gave 3.06 g (77%) of pure 14 as a colorless oil: NMR (DMSO- d_6) δ 7.10–6.98 (3 H, m), 4.31 (2 H, s), 3.63 (3 H, s), 3.24 (3 H, s), 3.00-2.68 (5 H, m), 2.15–2.00 (1 H, m), 1.80–1.64 (1 H, m); MS m/e 234.

2-Cyano-6-(methoxymethyl)-1,2,3,4-tetrahydronaphthalene (15). A solution of 14 (3.04 g, 13 mmol), tetrahydrofuran (40 mL), and borane-methyl sulfide complex (1 M in CH_2Cl_2) (19.5 mL, 19.5 mmol, 1.5 equiv) was refluxed for 4 h. After cooling to room temperature the mixture was poured into a saturated solution of K_2CO_3 . After extraction with diethyl ether (3 × 250 mL), the organic extract was washed with brine, dried (MgSO₄), and then concentrated in vacuo. The residual oil was chromatographed on silica gel with dichloromethane/diethyl ether 1:1 to yield 2.30 g (86%) of the alcohol intermediate as an oil: NMR (DMSO- d_6) δ 7.06-6.95 (3 H, m), 4.54 (1 H, t, J = 6 Hz), 4.34 (2 H, s), 3.38 (2 H, t, J = 6 Hz), 3.28 (3 H, s), 2.90-2.28 (4 H, m), 2.00-1.68 (2 H, m))H, m), 1.43-1.20 (1 H, m). A mixture of the crude alcohol (2.30 g, 11.2 mmol), DMSO (40 mL), and N-ethyldiisopropylamine (8.69 g, 67.2 mmol, 6 equiv) was stirred at 15-20 °C. Sulfur trioxidepyridine complex (10.76 g, 67.2 mmol, 6 equiv) was added in small portions over a period of 1 h. Finally, the mixture was stirred

for another hour at room temperature and the solution was then poured into a mixture of ice/2 N HCl (1:1, 500 mL). After extraction with dichloromethane $(3 \times 400 \text{ mL})$, the organic layers were dried (MgSO₄), and the solvent was removed in vacuo. The residue was flash chromatographed on silica gel with dichloromethane to yield 1.55 g (68%) of the aldehyde as a light yellow oil: NMR (DMSO- d_{6}) δ 9.70 (1 H, s), 7.13–7.00 (3 H, m), 4.32 (2 H, s), 3.25 (3 H, s), 2.95–2.70 (5 H, m), 2.17–2.07 (1 H, m), 1.77–1.63 (1 H, m). To a solution of the raw aldehyde (1.55 g, 7.60 mmol) in methyl alcohol (90 mL) was added sodium acetate (3.74 g, 45.6 mmol, 6 equiv) and hydroxylamine hydrochloride (2.64 g, 38.0 mmol, 5 equiv). The suspension was stirred at room temperature for 0.5 h. The reaction mixture was poured into brine (200 mL) and extracted with dichloromethane $(3 \times 100 \text{ mL})$. The organic extract was dried (MgSO₄) and then concentrated in vacuo. The residual crude "oxime" was dissolved in chloroform (60 mL). To this stirred solution was added 1,1'-carbonyldiimidazole (3.70 g, 22.8 mmol, 3 equiv) in small portions over a period of 30 min (0-5 °C). Finally, the reaction mixture was stirred at room temperature for an additional hour. The resulting mixture was poured into $2 \text{ N H}_3\text{PO}_4$ (200 mL) and then it was extracted with dichloromethane $(3 \times 100 \text{ mL})$. The combined extracts were washed with water and brine. The organic phase was dried $(MgSO_4)$ and the solvent was removed in vacuo. The residue was flash chromatographed on silica gel with dichloromethane, affording 0.89 g (58%) of pure 15 as white crystals: mp 48-49 °C; NMR (DMSO-d₆) § 7.12-7.03 (3 H, m), 4.33 (2 H, s), 3.32-2.75 (8 H, m), 2.10–1.91 (2 H, m); IR 2200 cm⁻¹ (CN); MS m/e 201.

2-Cyano-6-(iodomethyl)-1,2,3,4-tetrahydronaphthalene (16). To a solution of 15 (0.302 g, 1.5 mmol) in chloroform (15 mL) was added trimethylsilyl iodide (0.255 mL, 1.875 mmol, 1.25 equiv). The mixture was stirred at room temperature for 18 h (in the dark). Methyl alcohol (1 mL) was added and the solvent was removed in vacuo. The residue was treated with 2 M sodium pyrosulfite (100 mL). After extraction with diethyl ether (3 × 100 mL), the combined extracts were washed with 2 M NaHCO₃ and brine. The organic phase was dried (MgSO₄) and the solvent was removed in vacuo. The residue was flash chromatographed on silica gel with dichloromethane/hexane (1:1), affording after recrystallization from diethyl ether 0.35 g (79%) of pure 16: mp 123-124 °C; NMR (DMSO-d₆) δ 7.23 (1 H, d, J = 9 Hz), 7.18 (1 H, s), 7.06 (1 H, d, J = 9 Hz), 4.58 (2 H, s), 3.38-2.73 (5 H, m), 2.20-1.86 (2 H, m). Anal. (C₁₂H₁₂IN) C, H, N.

2-n-Butyl-4-chloro-5-(hydroxymethyl)-1-[(2-cyano-1,2,3,4-tetrahydronaphthalen-6-yl)methyl]imidazole (17a) and Its Regioisomer 17b. To a suspension of sodium hydride (55%, 51 mg, 1.16 mmol, 1.0 equiv) in dimethylformamide (4 mL) at 25 °C was added dropwise a solution of 2-n-butyl-4(5)chloro-5(4)-(hydroxymethyl)imidazole³ (219 mg, 1.16 mmol, 1.0 equiv) in dimethylformamide (4 mL). The resulting mixture was stirred at 25 °C for 1.5 h. To this mixture was added dropwise a solution of 16 (345 mg, 1.16 mmol) in dimethylformamide (3 mL) and the reaction mixture was stirred for another 30 min at room temperature. The solvent was removed in vacuo and the residue was poured into a mixture of ice/ H_2O . After extraction with dichloromethane (3 \times 100 mL), the combined extracts were dried $(MgSO_4)$, and the solvent was removed in vacuo. The residue was flash chromatographed over silica gel (elution: ethyl acetate/hexane 2:1), affording 228 mg (55%) of pure 17a as an oil $(R_f 0.49)$ and 124 mg (30%) of pure 17b also as an oil $(R_f 0.08)$.

17a: NMR (DMSO- d_6) δ 7.10 (1 H, d, J = 9 Hz), 6.85 (1 H, s), 6.80 (1 H, d, J = 9 Hz), 5.26–5.14 (3 H, m), 4.31 (2 H, d, J = 6 Hz), 3.36–2.35 (7 H, m), 2.15–1.85 (2 H, m), 1.46 (2 H, m), 1.25 (2 H, m), 0.80 (3 H, t, J = 7 Hz).

17b: NMR (DMSO- d_{g}) δ 7.10 (1 H, d, J = 9 Hz), 6.85 (1 H, s), 6.76 (1 H, d, J = 9 Hz), 5.10 (2 H, s), 4.89 (1 H, t, J = 6 Hz), 4.28 (2 H, d, J = 6 Hz), 3.36–2.65 (5 H, m), 2.56 (2 H, t, J = 7 Hz), 2.15–1.85 (2 H, m), 1.54 (2 H, m), 1.30 (2 H, m), 0.83 (3 H, t, J = 7 Hz).

2-*n*-Butyl-4-chloro-5-(hydroxymethyl)-1-[[2-(1*H*-tetrazol-5-yl)-1,2,3,4-tetrahydronaphthalen-6-yl]methyl]imidazole (18a). A mixture of 17a (220 mg, 0.61 mmol), tributyltin azide (405 mg, 1.22 mmol, 2 equiv), and xylene (8 mL) was refluxed for 18 h. The solvent was removed in vacuo and the residue was stirred with 1 N NaOH (20 mL) for 0.5 h. The aqueous mixture was extracted with diethyl ether (3×20 mL) to remove the tin compounds. After separation, the aqueous phase was acidified to pH 3 with 4 N HCl. The solid which precipitated was collected and gave after recrystallization from 2-propanol/ethyl acetate 180 mg (73%) of pure 18a as a white solid: mp 193-194 °C; NMR (DMSO- d_6) δ 7.08 (1 H, d, J = 9 Hz), 6.82 (1 H, s), 6.75 (1 H, d, J = 9 Hz), 5.18 (2 H, s), 4.30 (2 H, s), 3.29-2.66 (5 H, m), 2.48 (2 H, t, J = 7 Hz), 2.24-2.12 (1 H, m), 1.92-1.78 (1 H, m), 1.45 (2 H, m), 1.23 (2 H, m), 0.79 (3 H, t, J = 7 Hz). Anal. (C₂₀-H₂₅ClN₆O) C, H, Cl, N.

The following was analogously prepared.

2-n-Butyl-5-chloro-4-(hydroxymethyl)-1-[[2-(1*H*-tetrazol-5-yl)-1,2,3,4-tetrahydronaphthalen-6-yl]methyl]imidazole (18b). The title compound was prepared from 17b (114 mg, 0.32 mmol) to give after recrystallization from 2-propanol/ethyl acetate 104 mg (81%) of pure 18b as a white solid: mp 176-177 °C; NMR (DMSO- d_{e}) δ 7.08 (1 H, d, J = 9 Hz), 6.82 (1 H, s), 6.75 (1 H, d, J = 9 Hz), 5.10 (2 H, s), 4.28 (2 H, s), 3.29-2.70 (5 H, m), 2.57 (2 H, t, J = 7 Hz), 2.23-2.13 (1 H, m), 1.92-1.78 (1 H, m), 1.53 (2 H, m), 1.28 (2 H, m), 0.83 (3 H, t, J = 7 Hz). Anal. (C₂₀-H₂₅ClN₆O) C, H, Cl, N.

2-(Methoxycarbonyl)-2-methyl-6-(methoxymethyl)-1,2dihydronaphthalene (19). Small sodium pieces (0.794 g, 34.5 mmol, 3.5 equiv) were dissolved in liquid ammonia (75 mL) at -70 °C. After 10 min a solution of 8¹⁴ (2.13 g, 9.86 mmol) in anhydrous tetrahydrofuran (10 mL) was added dropwise at -70 to -63 °C (0.5 min). The reaction mixture was stirred at -70 °Cfor 3 min, and iodomethane (5 mL) was added in one portion. The reaction mixture was stirred for an additional 10 min at -70 °C. Thereafter an aqueous ammonium chloride solution (100 mL) was added. Ammonia was allowed to evaporate at 0 °C, water (100 mL) was added, and the aqueous solution was extracted with diethyl ether $(3 \times 200 \text{ mL})$. The organic phases were washed with water and brine and dried (MgSO₄), and the solvent was removed in vacuo. Flash chromatography of the remaining residue with dichloromethane gave 1.33 g (55%) of pure 19 as an oil: NMR (DMSO- d_{θ}) δ 7.18–7.06 (3 H, m), 6.52 (1 H, d, J = 10 Hz), 6.01 (1 H, d, J = 10 Hz), 4.34 (2 H, s), 3.62 (3 H, s), 3.28 (3 H, s), 3.18(1 H, d, J = 17 Hz), 2.78 (1 H, d, J = 17 Hz), 1.23 (3 H, s); MSm/e 246.

2-(Methoxycarbonyl)-2-methyl-6-(methoxymethyl)-1,2,3,4-tetrahydronaphthalene (20). To a solution of 19 (1.30 g, 5.28 mmol) and cobalt(II) chloride hexahydrate (1.26 g, 5.28 mmol, 1 equiv) in ethanol (50 mL) under Ar at 0 °C was added sodium borohydride (0.80 g, 21.1 mmol, 4 equiv) in portions. The solution became immediately dark and hydrogen evolved. The mixture was allowed to reach room temperature and was stirred for an additional hour. After removal of the solvent, the residue was poured into a mixture of ice/2 N HCl (1:1, 200 mL). The aqueous solution was extracted with dichloromethane (2×200) mL), the combined organic phases were dried $(MgSO_4)$, and the solvent was removed in vacuo. Flash chromatography of the remaining residue in dichloromethane gave 1.20 g (92%) of pure **20** as an oil: NMR (DMSO- d_6) δ 7.07–6.98 (3 H, m), 4.34 (2 H, s), 3.58 (3 H, s), 3.28 (3 H, s), 3.11 (1 H, d, J = 17 Hz), 2.83-2.65(2 H, m), 2.60 (1 H, d, J = 17 Hz), 2.10-2.00 (1 H, m), 1.77-1.67(1 H, m), 1.23 (3 H, s); MS m/e 248.

2-(Methoxycarbonyl)-2-methyl-6-(iodomethyl)-1,2,3,4tetrahydronaphthalene (21). To a solution of 20 (0.372 g, 1.5 mmol) in chloroform (15 mL) was added trimethylsilyl iodide (0.255 mL, 1.875 mmol, 1.25 equiv). The mixture was stirred at room temperature for 18 h in the dark. Methanol (1 mL) was added and the solvent removed in vacuo. The residue was treated with 2 M sodium pyrosulfite (100 mL) and was then extracted with diethyl ether (3 × 100 mL). The combined extracts were washed with 2 M NaHCO₃ and brine. The organic phase was dried (MgSO₄) and the solvent was removed in vacuo. The residue was flash chromatographed on silica gel with dichloromethane/hexane (1:1), affording 0.50 g (96%) of pure 21 as a light yellow oil: NMR (DMSO-d₆) δ 7.23-7.00 (3 H, m), 4.57 (2 H, s), 3.58 (3 H, s), 3.08 (1 H, d, J = 17 Hz), 2.87-2.60 (2 H, m), 2.56 (1 H, d, J = 17 Hz), 2.12-2.00 (1 H, m), 1.77-1.67 (1 H, m), 1.23 (3 H, s); MS m/e 344.

2-*n*-Butyl-4-chloro-5-(hydroxymethyl)-1-[[2-(methoxycarbonyl)-2-methyl-1,2,3,4-tetrahydronaphthalen-6-yl]methyl]imidazole (22a) and Its Regioisomer 22b. To a suspension of sodium hydride (55%, 66 mg, 1.50 mmol, 1 equiv) in dimethylformamide (4 mL) at 25 °C was added dropwise a solution of 2-n-butyl-4(5)-chloro-5(4)-(hydroxymethyl)imidazole³ (283 mg, 1.50 mmol, 1.0 equiv) in dimethylformamide (4 mL). The resulting mixture was stirred at 25 °C for 1.5 h, and then to this mixture was added dropwise a solution of 21 (516 mg, 1.50 mmol) in dimethylformamide (4 mL). Finally, the reaction mixture was stirred for 30 min at room temperature. The solvent was removed in vacuo and the residue was poured into a mixture of ice/H₂O. After extraction with dichloromethane (3 × 60 mL), the combined extracts were dried (MgSO₄), and the solvent was removed in vacuo. The residue was finally flash chromatographed over silica gel (elution: ethyl acetate/hexane 2:1), affording 276 mg (46%) of pure 22a as an oil (R_f 0.35) and 183 mg (30%) of pure 22b as an oil (R_f 0.08).

22a: NMR (DMSO- d_6) δ 7.06 (1 H, d, J = 9 Hz), 6.83 (1 H, s), 6.76 (1 H, d, J = 9 Hz), 5.20 (1 H, t, J = 6 Hz), 5.16 (2 H, s), 4.31 (2 H, d, J = 6 Hz), 3.58 (3 H, s), 3.10 (1 H, d, J = 17 Hz), 2.75–2.42 (5 H, m), 2.13 (1 H, m), 1.78–1.61 (1 H, m), 1.44 (2 H, m), 1.22 (2 H, m), 1.20 (3 H, s), 0.79 (3 H, t, J = 7 Hz).

22b: NMR (DMSO- d_6) δ 7.06 (1 H, d, J = 9 Hz), 6.80 (1 H, s), 6.76 (1 H, d, J = 9 Hz), 5.08 (2 H, s), 4.88 (1 H, t, J = 6 Hz), 4.30 (2 H, d, J = 6 Hz), 3.58 (3 H, s), 3.10 (1 H, d, J = 17 Hz), 2.75–2.49 (5 H, m), 2.13 (1 H, m), 1.78–1.61 (1 H, m), 1.50 (2 H, m), 1.28 (2 H, m), 1.20 (3 H, s), 0.81 (3 H, t, J = 7 Hz).

2-n-Butyl-4-chloro-5-(hydroxymethyl)-1-[(2-carboxy-2methyl-1,2,3,4-tetrahydronaphthalen-6-yl)methyl]imidazole (23a). A mixture of 22a (267 mg, 0.66 mmol), methyl alcohol (5 mL), water (2 mL), and 2 N NaOH (1.0 mL, 2.0 mmol, 3.03 equiv) was stirred at room temperature overnight. A 1.0-mL portion of 2 N HCl was added, and methyl alcohol was removed in vacuo. The residue was extracted with ethyl acetate $(2 \times 20 \text{ mL})$; the organic phases were washed with water and brine, dried $(MgSO_4)$, and then concentrated at reduced pressure. The precipitated crystals were recrystallized from ethyl acetate to yield 210 mg (81%) of pure 23a: mp 169-170 °C; NMR (DMSO-d₆) δ 12.30 (1 H, br s), 7.03 (1 H, d, J = 9 Hz), 6.80 (1 H, s), 6.73 (1 H, d)J = 9 Hz), 5.38–5.00 (1 H, m), 5.14 (2 H, s), 4.30 (2 H, s), 3.06 (1 H, d, J = 17 Hz), 2.75-2.67 (2 H, m), 2.54 (1 H, d, J = 17 Hz),2.47 (2 H, t, J = 7 Hz), 2.05–1.95 (1 H, m), 1.69–1.60 (1 H, m), 1.43 (2 H, m), 1.22 (2 H, m), 1.17 (3 H, s), 0.78 (3 H, t, <math>J = 7 Hz).Anal. (C₂₁H₂₇ClN₂O₃) C, H, Cl, N.

The following was analogously prepared.

2-*n*-Butyl-5-chloro-4-(hydroxymethyl)-1-[(2-carboxy-2methyl-1,2,3,4-tetrahydronaphthalen-6-yl)methyl]imida zole (23b) was prepared from 22b (175 mg, 0.43 mmol) to give after recrystallization from ethyl acetate 129 mg (77%) of pure 23b: mp 205-206 °C; NMR (DMSO- d_6) δ 12.30 (1 H, br s), 7.04 (1 H, d, J = 9 Hz), 6.78 (1 H, s), 6.73 (1 H, d, J = 9 Hz), 5.07 (2 H, s), 4.93-4.84 (1 H, m), 4.26 (2 H, m), 3.06 (1 H, d, J = 17 Hz), 2.73-2.52 (5 H, m), 2.05-1.95 (1 H, m), 1.69-1.60 (1 H, m), 1.52 (2 H, m), 1.28 (2 H, m), 1.17 (3 H, s), 0.82 (3 H, t, J = 7 Hz). Anal. ($C_{21}H_{27}ClN_2O_3$) C, H, Cl, N.

Molecular Modeling. Short Description of GRASP. The purpose of the program GRASP is to perform the superpositioning of one molecule upon another. The superpositioning can be either rigid, i.e. both molecules are treated as rigid bodies, or flexible, in which case torsion angles of one of the molecules are allowed to vary. Molecules can be input in the program as single conformers or sets of conformers. The superpositions are defined by specifying graphically on an Evans and Sutherland PS 300 terminal the atoms of the two molecules whose positions are to be matched. In the most general situation in which both molecules are input as multiple conformers, the program automatically performs the superposition of each conformer of the first molecule on each conformer of the second molecule. The output of the program is a file containing the superimposed molecules in their conformations which have given the lowest least-square-fit values in this systematic treatment. To give an idea of the speed of the program, the rigid-body superposition of two molecules input as sets of thirty conformers takes ca. 1 min of CPU time on a VAX 6320 computer. In the case of the application described in this article, the DuP 753 template molecule was introduced as a single conformer while the naphthalenic derivatives were introduced as sets of minimum-energy conformers. For each naphthalenic molecule considered, the program performed a rigid-body superposition of each of its minimized conformations on that of DuP 753 using the atoms belonging to the *n*-butylimidazole moieties and "dummy" atoms defining vectors perpendicular to the tetrazole rings during the matching procedure.

The atomic coordinates corresponding to the figures presented in this work are available upon request to the authors.

Biological Methods. Angiotensin II Receptor Binding. ¹²⁵I-labeled AII (2200 Ci/mmol) was obtained from Anawa (Wangen, Switzerland). Unlabeled AII was purchased from Bachem (Bubendorf, Switzerland). Bovine serum albumin (BSA) was from Fluka (Buchs, Switzerland). The peptidase inhibitors were from Novabiochem (Läufelfingen, Switzerland). The culture media was purchased from Amimed AG (Muttenz, Switzerland).

Membrane Preparation. The original primary culture of rat aorta smooth muscle cells (SMC) was obtained from Dr. Pfeilschifter (Ciba-Geigy, Basel, Switzerland). The cells were further grown on Dulbecco's Minimum Essential Medium (MEM) containing 4.5 g/L glucose and supplemented with 4 mM L-glutamine, 15% fetal calf serum, and penicillin-streptomycin (200 IU-200 μ g/mL). The cells were obtained after 5-20 passages, up to which no changes in AII-binding characteristics or AII-induced IP₃ formation were noted. At confluence, the cells were washed twice with phosphate-buffered saline (PBS) and harvested with a rubber policeman. The pellet was resuspended as described above. The membrane preparations were kept in liquid nitrogen or in aliquots at -80 °C until used; no apparent loss of AII-binding activity was seen under these conditions.

Binding Assay. The experiments were performed with an automatic pipetting and filtration device (Filter-Prep 101, Ismatec, Zurich, Switzerland). Briefly, $20-60 \mu g$ of protein was incubated at 25 or 30 °C for 60 min with radioactive tracer (150 pM) and varying concentrations of unlabeled competitors in the buffer used for resuspension of the pellet. The reaction was terminated by the addition of 2 mL of ice-cold buffer. Bound and free radioactivity were separated by immediate filtration through Whatman GF/F filters, which were washed three times with 2 mL of cold PBS. The radioactivity trapped on the filter was measured in a counter (Pharmacia-LKB, Uppsala, Sweden) at 80% efficiency.

Nonspecific binding was determined in the presence of 1 μ M unlabeled AII.

Data Analysis. The binding data were analyzed by using the four-parameter logistic dose-response method of De Lean et al.¹⁷ for the IC_{50} estimation.

Inhibition of Angiotensin II Induced Vasoconstriction in Rabbit Aortic Rings. Methods. Isolated Rabbit Thoracic Aorta Rings. Rabbits (2-2.5 kg, Chincilla, male) were stunned by a blow to the neck and the descending thoracic aorta quickly removed. From each aorta, rings 2-3 mm wide were prepared and mounted between two parallel hooks under an initial resting tension of 2 g. Thereafter rings were immersed in a 20-mL tissue bath containing a modified Krebs-Henseleit solution of the following composition (mM): 118 NaCl, 4.7 KCl, 2.52 CaCl₂, 24.8 NaHCO₃, 1.2 Mg₂SO₄, 1.2 KH₂PO₄, 10 glucose, at 37 °C, and gassed with 95% O_2 and 5% CO_2 . Each preparation was allowed to equilibrate for at least 1 h. Isometric responses were measured with a force transducer (K30, Hugo Sachs Electronics Freiburg, FRG) coupled to a tissue bath data acquisition system (Buxco Electronics, Inc., Sharon, CT). At 20-min interval, rings were challenged with 10 nM angiotensin II (Hypertensin-CIBA). Two control values to each agonist were obtained. Thereafter rings were incubated with graded concentrations of the test compound for 5 min prior to each agonist challenge. Three to four concentrations were tested for each preparation. Controls rings were incubatued with the vehicle (DMSO). Data were analyzed with the Buxco system and a software package (Branch Technology, Dexter, MI). Responses were expressed as a percentage of the initial control values. The concentration producing a 50% inhibition of the initial value is given as IC_{50} .

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Development of a Small RGD Peptide Fibrinogen Receptor Antagonist with Potent Antiaggregatory Activity in Vitro

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The development of potent antithrombotic agents from the fibrinogen platelet receptor binding sequences Fg- α 572-575 ·Arg-Gly-Asp-Ser- and Fg- γ 400-411 ·HHLGGAKQAGDV, believed to be a cryptic RGD-type sequence, is described. The tetrapeptide Ac-RGDS-NH₂ itself is capable of inhibiting platelet aggregation in vitro at high concentrations, IC₅₀ 91.3 ± 0.1 μ M [in vitro antiaggregatory activity employing dog platelet rich plasma (PRP)/ADP], due to low platelet fibrinogen receptor affinity, $K_1 2.9 \pm 1.9 \mu$ M (purified, reconstituted human platelet GPIIb/IIIa), relative to fibrinogen, $K_1 38.0 \pm 6.0$ nM. The peptide is also unstable to plasma, suffering total loss of in vitro activity upon incubation in PRP for 3 h ($T^{1/2}$ 90 min). Only modest improvements in potency were achieved with linear analogues of Ac-RGDS-NH₂, while dramatic results were achieved with cyclic analogues, culminating in the cyclic disulfide Ac-cyclo-S,S-[Cys-(N^a-Me)Arg-Gly-Asp-Pen]-NH₂ (SK&F 106760) with improved plasma stability (100% activity after 3 h), affinity (K_1 58 ± 20 nM purified human receptor), and potency (IC₅₀ 0.36 ± 0.4 μ M dog PRP/ADP). The affinity of this peptide is 2 orders of magnitude greater than that of Ac-RGDS-NH₂. The affinity of the analogue is also comparable to fibrinogen. This peptide constitutes a first potent small peptide entry into the class of novel antithrombotic agents called fibrinogen receptor antagonists.

Introduction

The most critical step in platelet aggregation is the cross-linking of activated platelets by the multifunctional plasma protein fibrinogen.¹ A logical approach toward

inhibition of aggregation and hence thrombus formation would be through inhibition of the binding of fibrinogen to its platelet receptor, the glycoprotein complex of GPIIb and GPIIIa.^{1,2} The first fibrinogen receptor antagonists

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