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 = CO_2CH_3), 61508-36-9; 1 (X = Cl, Y = NO_2), 97-09-6; 2 (X = Br, Y = H), 29619-31-6; 2 (X = Cl, Y = H), 29619-30-5; 2 (X = Cl, Y = CO_2CH_3), 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, 108966-56-9; 3h, 135832-41-6; 3i, 135832-42-7; 3j, 108966-54-7; 3k, 108966-73-0; 3l, 108966-70-7; 3m, 108966-76-3; 3n, 108966-74-1; 3o, 108966-77-4; 3p, 108966-75-2; 3q, 108966-78-5; 3r, 108966-58-1; 3s, 108966-59-2; 3t, 108966-60-5; 3u, 108966-65-0; 3v, 135832-43-8; 3w, 108966-62-7; 3x, 108966-68-3; 3y, 108966-66-1; 3z, 108966-67-2; 3aa, 135832-44-9; 4a, 135832-45-0; 4b, 108966-61-6; 5a, 53595-65-6; 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, 135832-52-9; 12d, 135832-53-0; 12e, 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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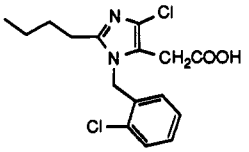
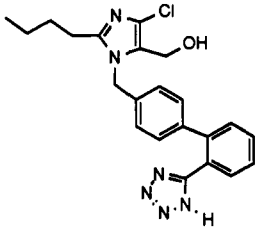
Starting from the structure of the novel nonpeptidic angiotensin II antagonist DuP 753, a series of more rigid analogues was prepared by replacing the biphenyl part of DuP 753 with a naphthalene ring. Five different regioisomers (compounds **6a–e**) were synthesized, and receptor binding in rat smooth 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 expectation of getting a further increase in potency. Whereas the carboxylic acid derivatives **13a,b** showed activity in 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 AT_1 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 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 receptor[6] 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 groups—substituted imidazole and acid function—at the site of the AT_1 receptor.

Table I. Distances between the Centers of Tetrazole Rings in Figure 1 Superpositions

compd	distance, Å	compd	distance, Å
6a	1.1	**6d**	2.4
6b	3.3	**6e**	2.0
6c	2.8		

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

(1) 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.
(6) According to Bumpus et al. (*Hypertension*, in press), the two known AII receptor subtypes are named AT_1 and AT_2. All vascular effects of AII seem to be mediated via the AT_1 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.

0022-2623/91/1834-3105$02.50/0

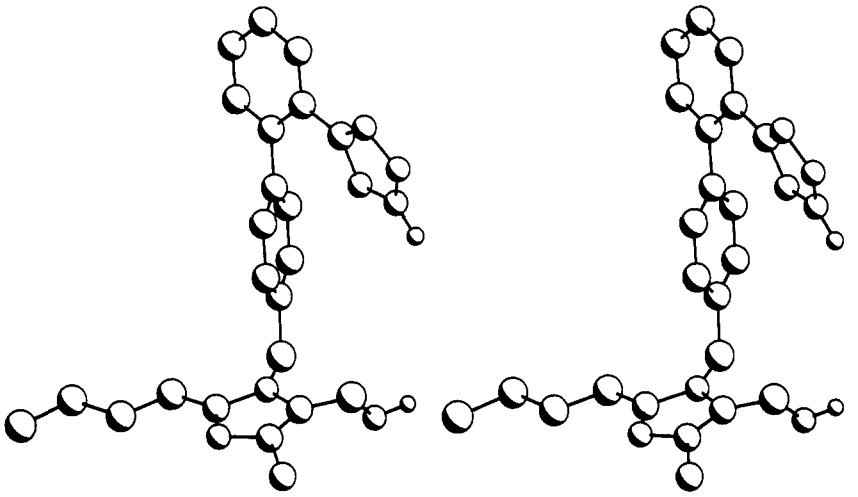


Figure 1. Stereoplot of DuP 753, assumed bioactive conformation.

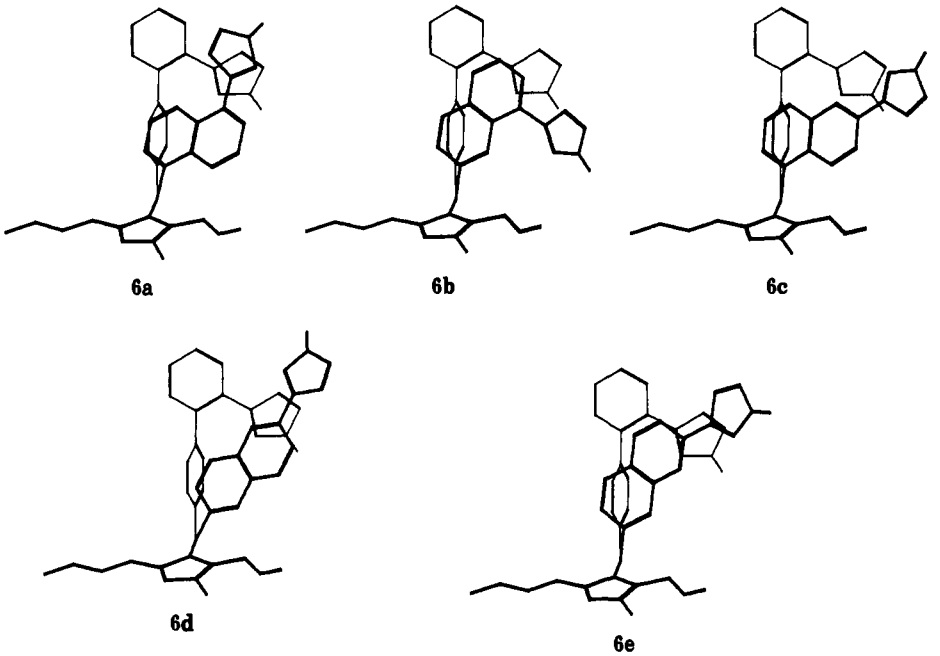


Figure 2. Naphthalenic derivatives **6a–e** (thick line) superimposed on DuP 753 (thin line). Parts of the naphthalenic moieties of these compounds are located in regions of space not occupied by DuP 753. If one classes the molecules according to which region of space their naphthalene ring occupies, 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 program[7] and were subsequently minimized in BATCHMIN[8] employing the NCC force field.[9] Then, by using the program GRASP,[10] the calculated low-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 AT_1 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.

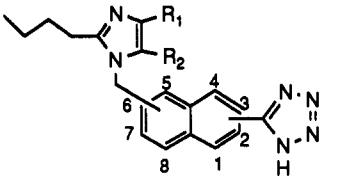
(7) CONCEPTOR: in-house molecular modeling program written by N.C. Cohen, similar to SCRIPT: Cohen, N. C.; Colin, P.; Lemoine, G. *Tetrahedron* **1981**, *37*, 1711.

(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.

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



compd	R_1	R_2	position of tetrazole subst	position of imidazole subst	binding IC_{50},[a] μM	rabbit aortic ring IC_{50},[a] μM	mp, °C	anal.
6a	Cl	CH_2OH	1	5	1.1	0.7	168–170	C, H, Cl, N
6b	Cl	CH_2OH	1	7	55	nt[b]	178–179	C, H, Cl, N
6c	Cl	CH_2OH	2	5	4.1	2.6	209–211	C, H, Cl, N
6d	Cl	CH_2OH	2	6	0.6	1.6	212–214	C, H, Cl, N
6e	Cl	CH_2OH	2	7	20	nt	189–191	C, H, Cl, N
7	CH_2OH	Cl	2	6	0.2	0.12	197–199	C, H, Cl, N
DuP 753					0.026	0.024		

[a] All tests were performed in duplicate. For details see the Experimental Section. [b] Not 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) isomer (assignment based on proton NMR). The 2,6-substituted tetrahydronaphthalene derivatives (Table II)

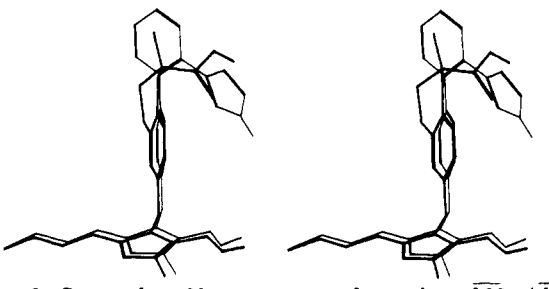
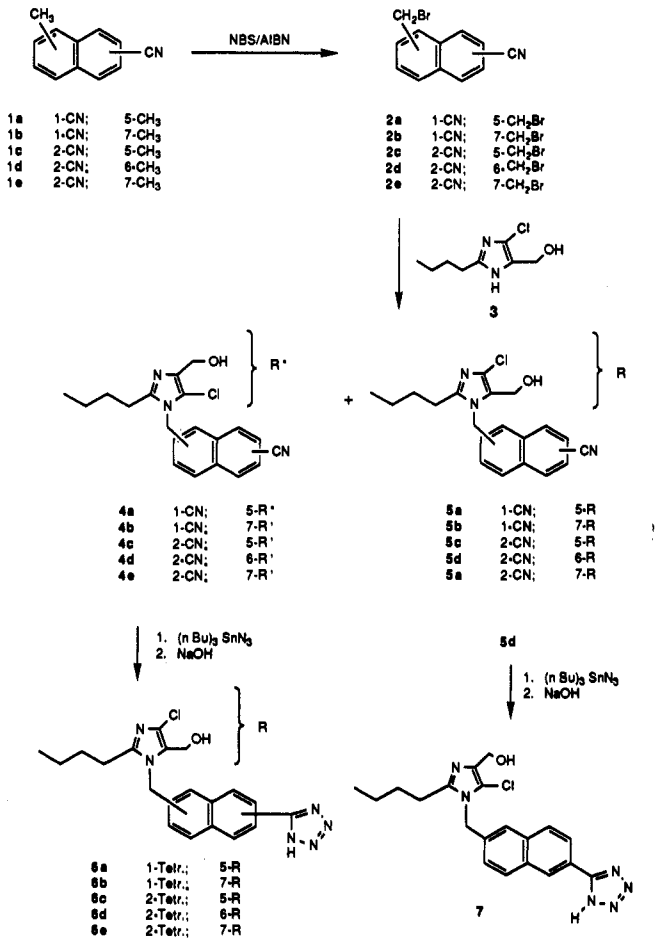


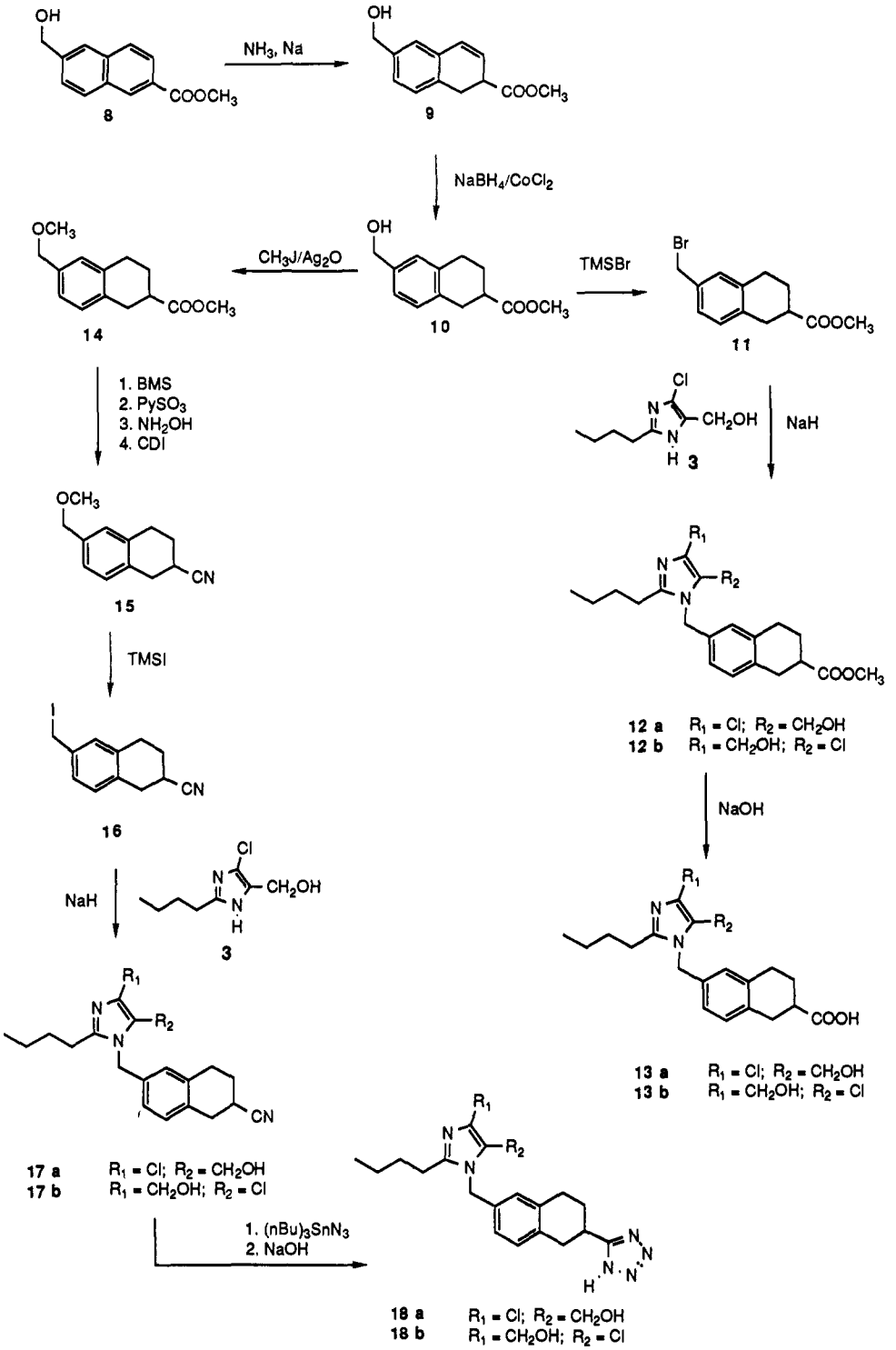
Figure 3. Stereoplot of low-energy conformation of **23a** (thick line) that fits best the assumed active conformation of DuP 753 (thin line).

Scheme I



(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



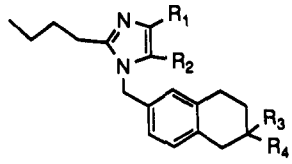
were obtained via a Birch reduction of the known hydroxymethyl ester 8[14] (Scheme II). The double bond in position 3,4 was reduced very cleanly by using the sodium borohydride–cobalt chloride complex. Direct conversion of the resulting benzylic alcohol **10** with trimethylbromosilane in chloroform 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

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

(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.

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

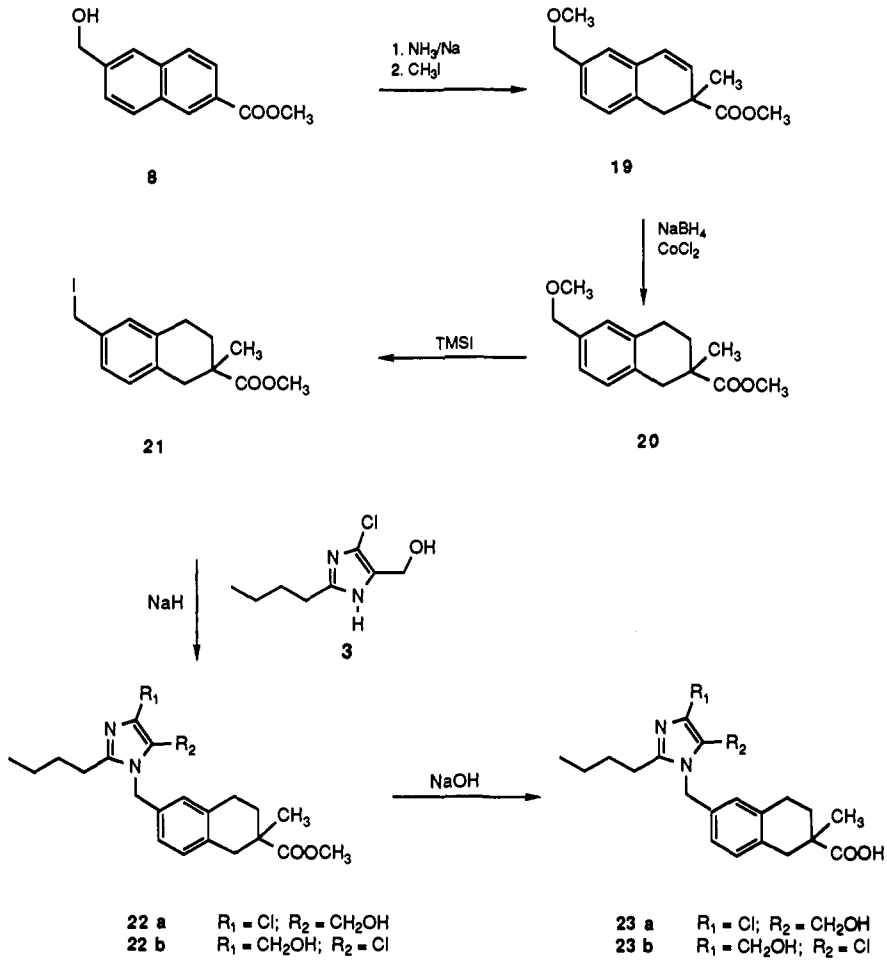
Table III. Tetrahydronaphthalene Derivatives: Receptor Binding Activity and Inhibition of All Induced Contractions in Rabbit Aortic Rings



compd	R_1	R_2	R_3	R_4	binding IC_{50},[a] μM	rabbit aortic ring IC_{50},[a] μM	mp, °C	anal.
13a	Cl	CH_2OH	COOH	H	8.9	1.2	175–177	C, H, Cl, N
13b	CH_2OH	Cl	COOH	H	1.1	0.3	212–214	C, H, Cl, N
18a	Cl	CH_2OH	2-tetrazolyl	H	5.4	1.9	193–194	C, H, Cl, N
18b	CH_2OH	Cl	2-tetrazolyl	H	1.4	0.56	166–168	C, H, Cl, N
23a	Cl	CH_2OH	COOH	CH_3	4.6	2.2	169–170	C, H, Cl, N
23b	CH_2OH	Cl	COOH	CH_3	2.8	2.7	205–206	C, H, Cl, N
DuP 753					0.026	0.024		

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

Scheme III



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, see ref 17).

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.

(18) De Lean, A.; Munson, P. J.; Rodbard, D. *Am. J. Physiol.* **1978**, *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_6) δ 8.58 (1 H, d, J = 9 Hz), 8.24 (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. ($C_{12}H_9BrN$) 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. ($C_{12}H_9BrN$) C, H, Br, N.

2-Cyano-5-(bromomethyl)naphthalene (2c) was prepared from **1c**[13] (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. ($C_{12}H_8BrN$) 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. ($C_{12}H_8BrN$) 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)imidazole[3] (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 ($MgSO_4$) 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_f (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. ($C_{20}H_{20}ClN_3O$) 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. ($C_{20}H_{20}ClN_3O$) 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. ($C_{20}H_{20}ClN_3O$) 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. ($C_{20}H_{20}ClN_3O$) 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_6) δ 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. ($C_{20}H_{20}ClN_3O$) C, H, Cl, N.

5c: mp 179–180 °C; NMR (DMSO-d_6) 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).

Anal. ($C_{20}H_{20}ClN_3O$) 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: 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. ($C_{20}H_{20}ClN_3O$) C, H, Cl, N.

5d: mp 144–145 °C; NMR (DMSO-d_6) δ 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. ($C_{20}H_{20}ClN_3O$) 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_6) δ 8.56 (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. ($C_{20}H_{20}ClN_3O$) C, H, Cl, N.

5e: mp 131–132 °C; NMR (DMSO-d_6) 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. ($C_{20}H_{20}ClN_3O$) C, H, Cl, N.

2-*n*-Butyl-4-chloro-5-(hydroxymethyl)-1-[[1-(1*H*-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 × 50 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) δ 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. ($C_{20}H_{21}ClN_6O$) C, H, Cl, N.

2-*n*-Butyl-4-chloro-5-(hydroxymethyl)-1-[[2-(1*H*-tetrazol-5-yl)naphthalen-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_6) δ 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. ($C_{20}H_{21}ClN_6O$) C, H, Cl, N.

2-*n*-Butyl-4-chloro-5-(hydroxymethyl)-1-[[2-(1*H*-tetrazol-5-yl)naphthalen-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-d_6) 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. ($C_{20}H_{21}ClN_6O$) 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. ($C_{20}H_{21}ClN_6O$) 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 **8**[14] (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 × 600 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 = 2.5/10 Hz), 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).

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 × 500 mL). The organic layer was dried ($MgSO_4$), 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_6) 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 ($MgSO_4$), 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-d_6) 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)imidazol[3] (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/H_2O. 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 ($MgSO_4$) 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 CH_2Cl_2/MeOH 9:1) and 0.25 g (35%) of **12b** as a light yellow oil (R_f 0.46 in CH_2Cl_2/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 ($MgSO_4$), 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-d_6) 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. ($C_{20}H_{25}ClN_2O_3$) 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. ($C_{20}H_{25}ClN_2O_3$) 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 ($MgSO_4$), 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), 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 trioxide–pyridine 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 × 400 mL), the organic layers were dried ($MgSO_4$), 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 × 100 mL). The organic extract was dried ($MgSO_4$) 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 N H_3PO_4 (200 mL) and then it was extracted with dichloromethane (3 × 100 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-d_6) δ 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 $NaHCO_3$ 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/hexane (1:1), affording after recrystallization from diethyl ether 0.35 g (79%) of pure **16**: mp 123–124 °C; NMR (DMSO-d_6) 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. ($C_{12}H_{12}IN$) 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)imidazole[3] (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 × 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_6) 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. ($C_{20}H_{25}ClN_6O$) 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_6) 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. ($C_{20}H_{25}ClN_6O$) C, H, Cl, N.

2-(Methoxycarbonyl)-2-methyl-6-(methoxymethyl)-1,2-dihydronaphthalene (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 **8**[14] (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 °C for 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 × 200 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 with dichloromethane gave 1.33 g (55%) of pure **19** as an oil: NMR (DMSO-d_6) 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); MS m/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)-1,2,3,4-tetrahydronaphthalene (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 $NaHCO_3$ 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/hexane (1:1), affording 0.50 g (96%) of pure **21** as a light yellow oil: NMR (DMSO-d_6) 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)imidazole[3] (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/H_2O. After extraction with dichloromethane (3 × 60 mL), the combined extracts were dried ($MgSO_4$), 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-2-methyl-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 × 20 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-d_6) 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, J = 7 Hz). Anal. ($C_{21}H_{27}ClN_2O_3$) C, H, Cl, N.

The following was analogously prepared.

2-*n*-Butyl-5-chloro-4-(hydroxymethyl)-1-[(2-carboxy-2-methyl-1,2,3,4-tetrahydronaphthalen-6-yl)methyl]imidazole (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. ^{125}I-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 μg/mL). The cells were obtained after 5-20 passages, up to which no changes in AII-binding characteristics or AII-induced IP_3 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 μg 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 μM 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 $CaCl_2$, 24.8 $NaHCO_3$, 1.2 Mg_2SO_4, 1.2 KH_2PO_4, 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-NH_2 itself is capable of inhibiting platelet aggregation in vitro at high concentrations, IC_{50} 91.3 ± 0.1 μM [in vitro antiaggregatory activity employing dog platelet rich plasma (PRP)/ADP], due to low platelet fibrinogen receptor affinity, K_i 2.9 ± 1.9 μM (purified, reconstituted human platelet GPIIb/IIIa), relative to fibrinogen, K_i 38.0 ± 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-NH_2, while dramatic results were achieved with cyclic analogues, culminating in the cyclic disulfide Ac-cyclo-*S,S*-[Cys-(N^{α}-Me)Arg-Gly-Asp-Pen]-NH_2 (SK&F 106760) with improved plasma stability (100% activity after 3 h), affinity (K_i 58 ± 20 nM purified human receptor), and potency (IC_{50} 0.36 ± 0.4 μM dog PRP/ADP). The affinity of this peptide is 2 orders of magnitude greater than that of Ac-RGDS-NH_2. 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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