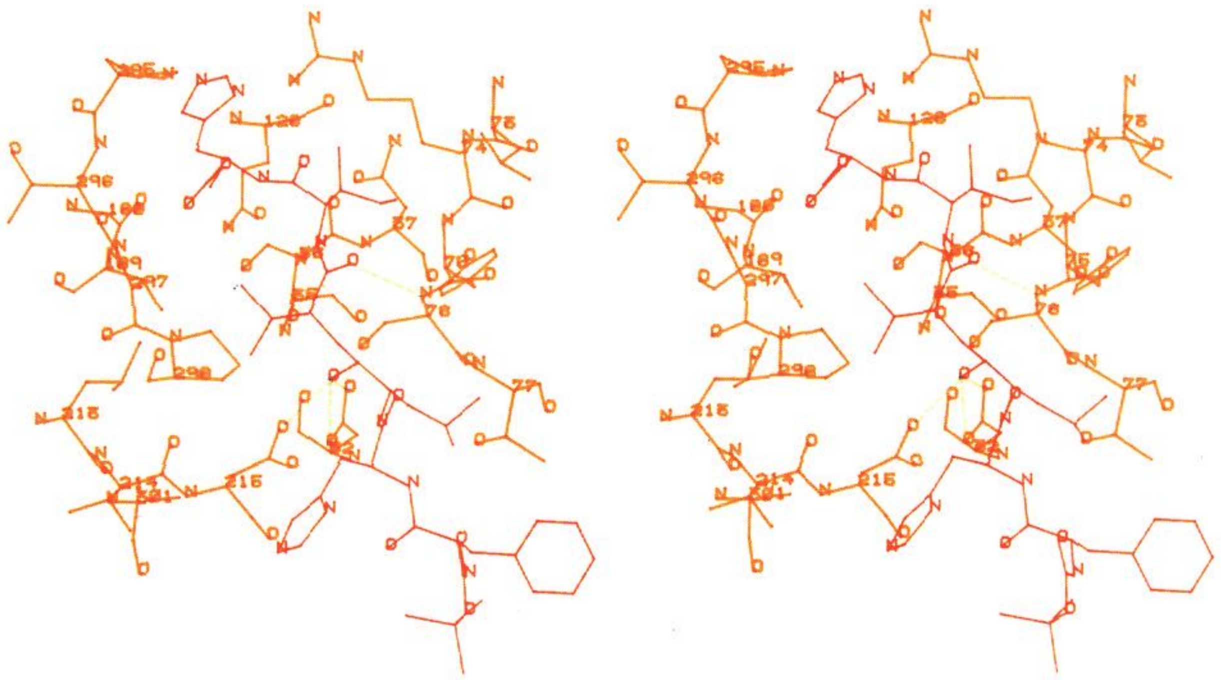
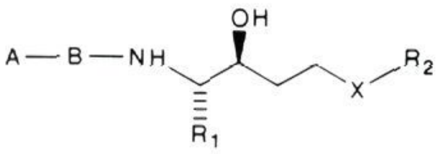


Figure 1. Stereoview of compound II (red) in the model active site of renin (orange). Note the relevant hydrogen bonds (dashed green lines) between the P_1 hydroxyl and the active site aspartates and between the Val P_1' carbonyl oxygen and the α-NH of Ser-76 as discussed in the text.

Table I. Dipeptide Analogues of Angiotensinogen



compd	A	B	R_1	CO	R_2	mp, °C	formula[a]
6	Boc-Phe	Ala	isobutyl	CO	$i\text{-}C_5H_{11}$	137–138	$C_{31}H_{51}N_3O_6$
7	Boc-Phe	Ala	isobutyl	CHOH[b]	$i\text{-}C_5H_{11}$	129–133	$C_{31}H_{53}N_3O_6$
12a	Boc-Phe	Ala	isobutyl	S	$i\text{-}C_5H_{11}$	137–138	$C_{30}H_{51}N_3O_5S$
12b	Boc-Phe	Ala	isobutyl	S	CH_2CH_2Ph	glass	$C_{33}H_{49}N_3O_5S$
12c	Boc-Phe	Ala	isobutyl	S	$i\text{-}C_4H_9$	137–139	$C_{29}H_{49}N_3O_5S$
12d	Boc-Phe	Ala	isobutyl	S	$i\text{-}C_3H_7$	126–128	$C_{28}H_{47}N_3O_5S$
13	Boc-Phe	Ala	isobutyl	SO[b]	$i\text{-}C_5H_{11}$	150–153	$C_{30}H_{51}N_3O_6S$
14a	Boc-Phe	Ala	isobutyl	SO_2	$i\text{-}C_5H_{11}$	165–166	$C_{30}H_{51}N_3O_7S$
14b	Boc-Phe	Ala	isobutyl	SO_2	CH_2CH_2Ph	186–187	$C_{33}H_{49}N_3O_7S$
14c	Boc-Phe	Ala	isobutyl	SO_2	$i\text{-}C_4H_9$	147–149	$C_{29}H_{49}N_3O_7S$
14d	Boc-Phe	Ala	isobutyl	SO_2	$i\text{-}C_3H_7$	156–158	$C_{28}H_{47}N_3O_7S$
21a	Boc-Phe	His	cyclohexylmethyl	SO_2	$i\text{-}C_3H_7$	145–147	$C_{34}H_{53}N_5O_7S$
21b	Boc-Phe	His	cyclohexylmethyl	SO_2	C_2H_5	158–160	$C_{33}H_{51}N_5O_7S$
22a	Boc-Phe	Ala	cyclohexylmethyl	SO_2	$i\text{-}C_3H_7$	92–94	$C_{31}H_{51}N_3O_7S$
22b	Boc-Phe	Ala	cyclohexylmethyl	SO_2	C_2H_5	150–151	$C_{30}H_{49}N_3O_7S$
23	Boc-Phe	Leu	cyclohexylmethyl	SO_2	$i\text{-}C_3H_7$	152–154	$C_{34}H_{57}N_3O_7S$
24	Boc-Phe	Phe	cyclohexylmethyl	SO_2	$i\text{-}C_3H_7$	139–141	$C_{37}H_{55}N_3O_7S$[c]
25	Boc-(Me)Tyr[d]	His	cyclohexylmethyl	SO_2	$i\text{-}C_3H_7$	160–162	$C_{35}H_{55}N_5O_8S$
26	Tba-Phe[e]	His	cyclohexylmethyl	SO_2	$i\text{-}C_3H_7$	146–148	$C_{35}H_{55}N_5O_6S$
27	Etoc-Phe[f]	His	cyclohexylmethyl	SO_2	$i\text{-}C_3H_7$	168–170	$C_{32}H_{49}N_5O_7S$

[a] All compounds gave satisfactory C, H, and N analyses. [b] *R, S* mixture of diastereomers at this center. [c] C: calcd, 64.79; found, 64.36. [d] (*tert*-Butyloxycarbonyl)tyrosine methyl ether. [e] (*tert*-Butylacetyl)phenylalanine. [f] (Ethoxycarbonyl)phenylalanine.

ethylene ketal was followed by hydrolysis with $Ba(OH)_2$ to give amino alcohol **5**. Mixed anhydride coupling of **5** with Boc-Phe-Ala-OH then gave the desired product **6**. The corresponding diol derivative **7** was prepared by $NaBH_4$ reduction of **6**.

Analogues containing a sulfur atom in the side chain and an isobutyl substituent at the P_1 subsite were prepared as outlined in Scheme II. Oxazolidinone **8** was synthesized analogously to **1** described above. Hydroboration of **8** with 9-BBN[12] afforded alcohol **9**, which gave thioethers **10a–d** by successive mesylation and mercaptide displacement. Oxazolidinone hydrolysis was followed by peptide coupling to complete the synthesis. The sulfoxide analogue **13** and sulfones **14a–d** were prepared by oxidation of the corresponding sulfides with MCPBA.

The syntheses of analogues containing a cyclohexylmethyl side chain at the P_1 subsite[13] were carried out as depicted in Scheme III. Dibal reduction of *N*-Boc-L-cyclohexylalanine methyl ester[14] was followed by in situ reaction of the resulting aldehyde with vinylmagnesium bromide to give oxazolidinone **15** in 54% yield. Hydroboration and mesylation as described above provided mesylate **17**. Displacement of **17** with isopropyl mercaptide and ethyl mercaptide produced **18a** and **18b**, respectively.

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(12) Brown, H. C.; Krishnamurthy, S.; Yoon, N. M. *J. Org. Chem.* **1976**, *41*, 1778.

(13) The inhibitor residues are numbered after Schechter and Berger: Schechter, I.; Berger, A. *Biochem. Biophys. Res. Commun.* **1967**, *27*, 157.

(14) Boger, J.; Payne, L. S.; Perlow, D. S.; Lohr, N. S.; Poe, M.; Blaine, E. H.; Ulm, E. H.; Schorn, T. W.; LaMont, B. I.; Lin, T.-Y.; Kawai, M.; Rich, D. H.; Veber, D. F. *J. Med. Chem.* **1985**, *28*, 1779.

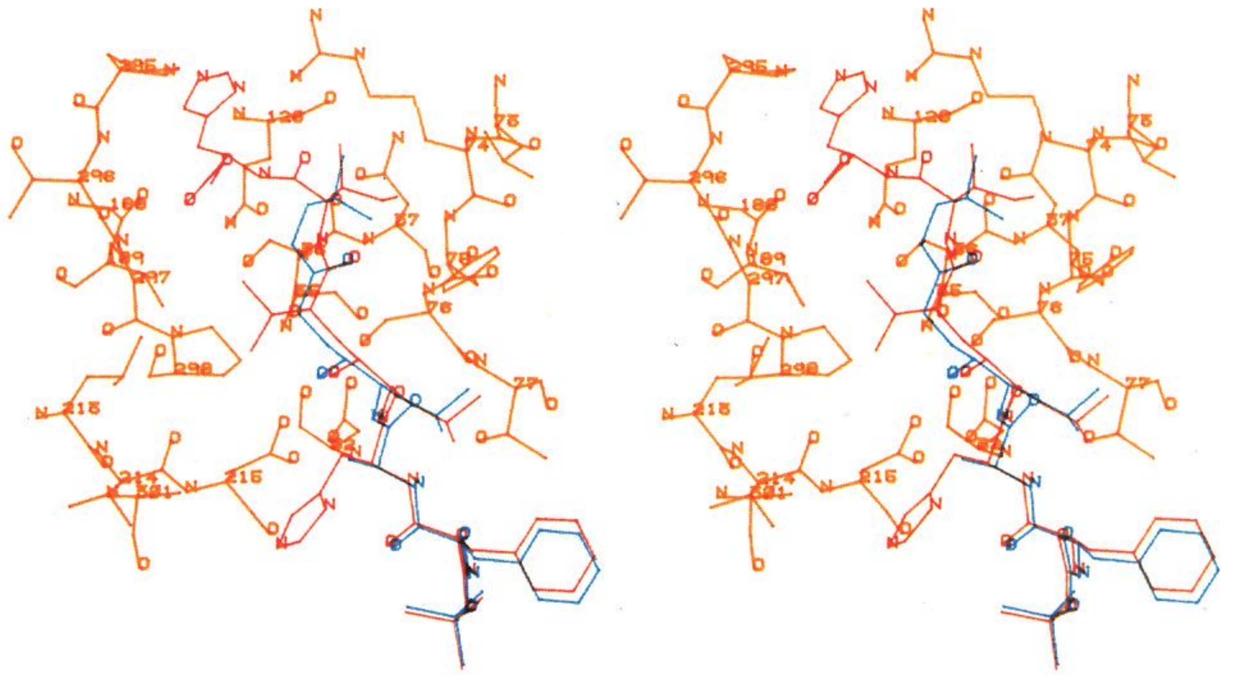


Figure 2. Stereoview of inhibitor **6** (blue) superimposed on compound II (red) in the active site of renin (orange). The renin active site was minimized along with the inhibitor **6**, but since the structure of the former did not change significantly, for purpose of comparison the enzyme structure in this figure is the same as in Figure 1.

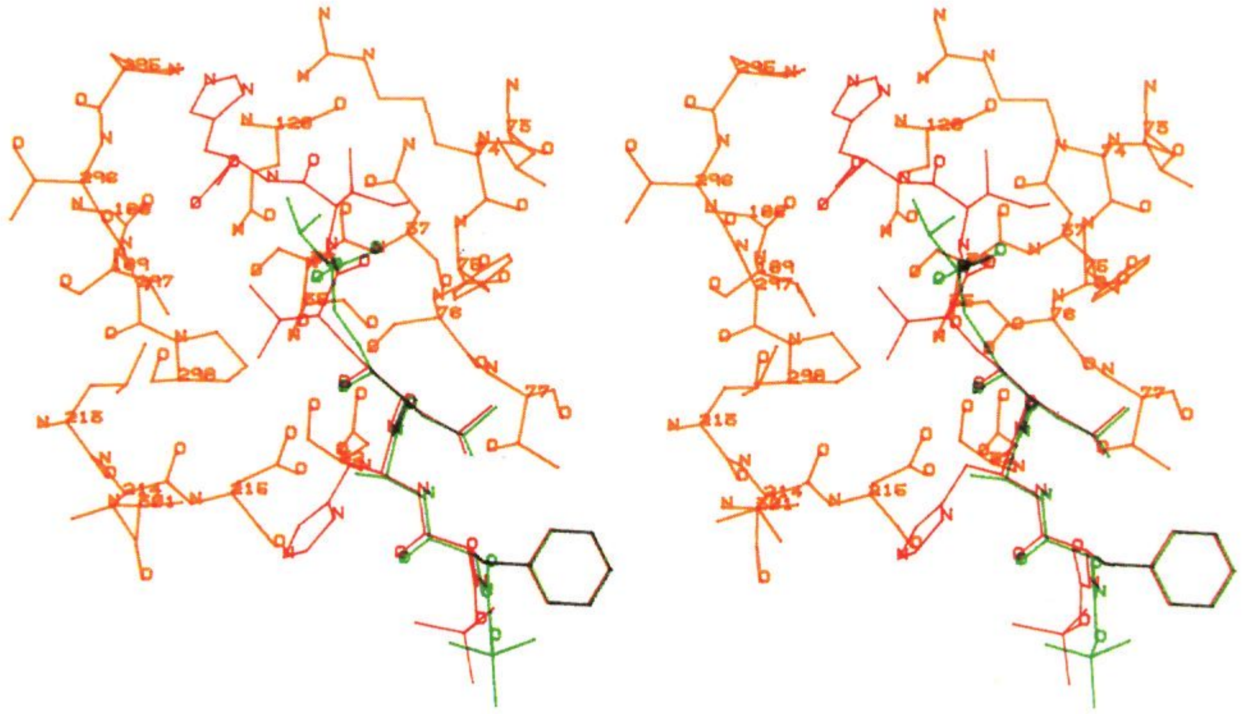
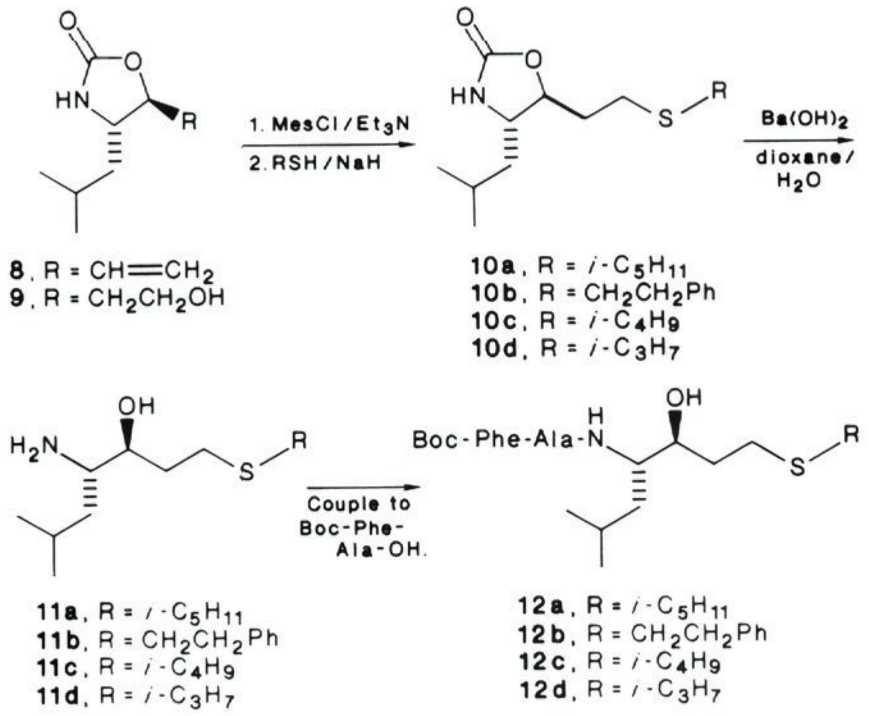


Figure 3. Stereoview of inhibitor **14d** (green) superimposed on compound II (red) in the active site of renin (orange). The renin active site was minimized along with inhibitor **14d**, but since the structure of the former did not change significantly, for purpose of comparison the enzyme structure in this figure is the same as in Figure 1.

Scheme II



Oxidation to the corresponding sulfones and oxazolidinone cleavage with Ba(OH)$_2$ led to amino alcohols **20a** and **20b**. Coupling of these products, either stepwise or with the appropriate dipeptides, then gave the desired final products.

The hydroxyl stereochemistry for the above products was established by examining the ^{1}H NMR spectra for the corresponding 2-oxazolidinones. The chemical shifts and coupling constants of ring hydrogens for the desired trans oxazolidinones are consistent with ample literature precedent.[15]

Biological Results and Discussion

Structure–Activity Relationships. Previously[5] we reported the effect of peptide chain length on renin in-

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(15) (a) Rich, D. J.; Sun, E. T. O. *J. Med. Chem.* **1980**, *23*, 27. (b) Futagawa, S.; Inui, T.; Shiba, T. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 3308. (c) Foglia, T. A.; Swern, D. *J. Org. Chem.* **1969**, *34*, 1680. (d) Cardillo, G.; Orena, M.; Sandri, S.; Tomasini, C. *Tetrahedron* **1985**, *41*, 163.