Dipeptide Analogues. Synthesis of a Potent Renin Inhibitor

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The synthesis of a potent renin inhibitor containing a dipeptide analogue and the amino acid statine is described.

The discovery of highly potent[1,2] (IC_{50} = 10^{-9}—10^{-8} M) competitive inhibitors of renin in which statine, (3*S*,4*S*)-4-amino-3-hydroxy-6-methylheptanoic acid, Sta, is incorporated into analogues of the porcine renin substrate has provided the impetus for an extensive study of this novel class of compounds. In connection with this, significant progress has been made in the preparation of an additional series of peptides which block the renin reaction.[2] The common feature of these renin inhibitors is the mechanistically important statine residue flanked by varying numbers of amino acids, see Table 1. Although decreasing peptide chain length might be expected to result in less potent renin inhibitors,[3] we focused on the synthesis of shorter peptides† (*i.e.*, fewer than five amino acids) containing nonpeptidal segments in an effort to increase the duration of action and oral activity.

Dipeptides in which the amide bond linkage has been replaced by some structural analogue have been used as a device to prepare metabolically stable peptides and mechanism-based enzyme inhibitors.[4] Considering the high substrate specificity exhibited by renin, we postulated that the geometric disposition of substituents attached to a dipeptide analogue would have to approximate closely those of the parent dipeptide. Furthermore, the configuration of any asymmetric centres in the analogue should be defined. Based on these considerations and the demonstration in these laboratories that the γ-amino acid statine is a surprisingly effective replacement for the Leu-Leu dipeptide in a number of potent renin inhibitors,[1,2] the heptanoic acid derivative (**4**) was prepared. This compound, intended to mimic Leu-Phe-NH_2 (**5**), was then elaborated to the renin inhibitor (**6**), a prototype designed to meet the aforementioned requirements.

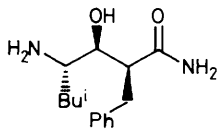
The Leu-Phe amide analogue (**4**) was prepared enantiospecifically, in protected form, in the following manner. Metallation of the *N*-acyloxazolidinone (**7**)[5] ($[\alpha]_D$ −69°, *c* 2.6, $CHCl_3$) with lithium di-isopropylamide (tetrahydrofuran, THF, −60 °C, 5.5 h) afforded the corresponding lithium enolate which reacted with Boc-L-leucine anhydride (inverse addition) to yield the ketone (**8**) in 45% yield (55% conversion).[6] This material was immediately reduced with zinc borohydride (−25 °C, Et_2O, 1.5 h) to afford the crystalline (2*S*,3*S*,4*S*)-alcohol (**9**) (89%, m.p. 149—151 °C, $[\alpha]_D$ −96°, *c* 0.3, EtOH).‡

Table 1. Inhibition of human renin by statine-containing substrate analogues.

Substrate analogue	K_I/M
(**1**) Boc-His-Pro-Phe-His-Sta-Leu-Phe-NH_2	2.3×10^{-9}
(**2**) Boc-Phe-His-Sta-Leu-Phe-NH_2	1.9×10^{-7}
(**3**) Boc-Phe-Phe-Sta-Leu-Phe-NH_2	4.8×10^{-9}

† The minimum kinetically competent substrate for renin around the cleavage site is an octapeptide (6—13); see ref. 3.

‡ Single crystal *X*-ray analyses of chiral oxazolidinone derivatives of (**9**) (2-n-butyl substituted for 2-benzyl) formed the basis of assignment in the whole series. These results will be disclosed in the full report.



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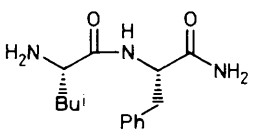

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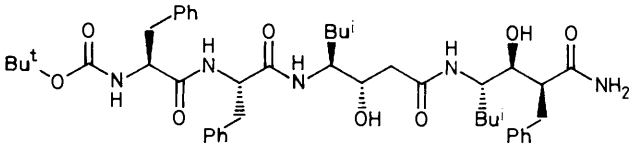

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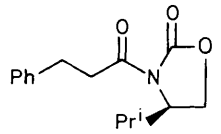

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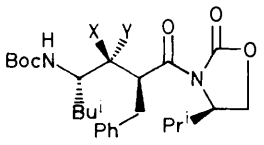
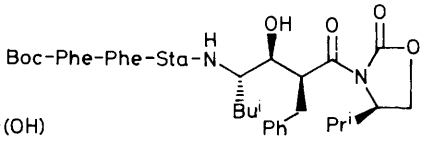


(8), X = Y = O
(9), X = OH, Y = H



Boc-Phe-Phe-Sta-(OH)
(10)

(11)

Further elaboration of the protected dipeptide analogue (**9**) [HCl, EtOAc, 0 °C then coupling to (**10**), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, 1-hydroxybenzotriazole, dimethylformamide] gave (**11**) (63% overall, m.p. 190—192 °C, $[\alpha]_D$ −52°, *c* 0.2, EtOH) which was converted in two synthetic operations (hydrazine, THF, 23 °C, then isopentyl nitrite, NH_4Cl, −20 °C) into the title compound (**6**) (47% overall, m.p. 137—139 °C, $[\alpha]_D$ −43.1°, *c* 0.25, EtOH).

Biological assay of the peptide (**6**) indicated a K_I value of 3.1×10^{-8} M against human kidney renin (pH 7.2, 37 °C).[7] The potency of (**6**) compares favourably with that of the peptides shown in Table 1, whose sequences more closely resemble that of angiotensinogen. In fact, (**6**) is the most potent peptide renin inhibitor reported having fewer than five amino acid residues. Substitution of (**4**) for Leu-Phe-NH_2 is, therefore, acceptable and augurs well for the design and synthesis of other peptide analogues and their incorporation into renin inhibitors.

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