Potent Human Renin Inhibitors containing Novel Small Cyclic Peptides and Stable to Chymotrypsin Degradation

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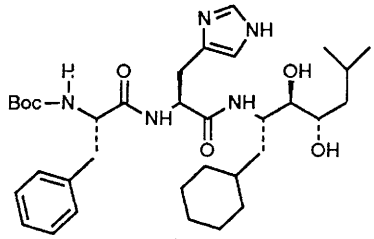
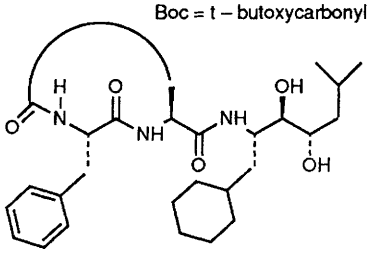
The synthesis of a novel series of tripeptides with 14- to 16-membered rings containing a urea linkage, which are potent human renin inhibitors and stable to the chymotrypsin degradation, is described.

The search for a renin inhibitor as an antihypertensive agent is a challenging target for medicinal chemists.[1] A new class of renin inhibitors characterized by the presence of a glycol function replacing the scissile amide bond of angiotensinogen has been reported.[2] A prototypical compound of this class is shown as structure (**1**). The high binding potency of (**1**) (IC_{50} 1.5 nM) for human renin is also accompanied by a facile degradation by the serine protease chymotrypsin (which rapidly cleaved these compounds between the phenylalanine and histidine residues *in vitro* in <5 min). Since stability to proteolytic enzymes is thought to be a requirement for developing orally active peptides, we sought to identify analogues of (**1**) that are stable to degrading enzymes and retain a high inhibitory potency for human renin. Towards this goal, a series of small cyclic tripeptides coupled to the glycol function represented by the generic structure (**2**) was synthesized. We envisage that these should be stable to chymotrypsin cleavage owing to our previous experience with other cyclic peptides.[3]



(**1**)

Boc = t – butoxycarbonyl



(**2**)

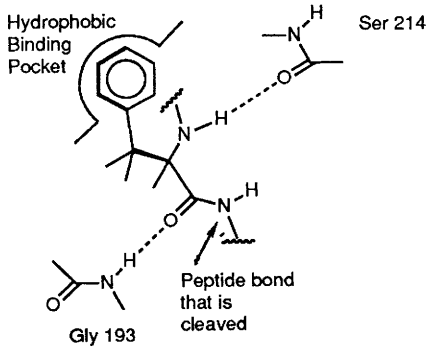
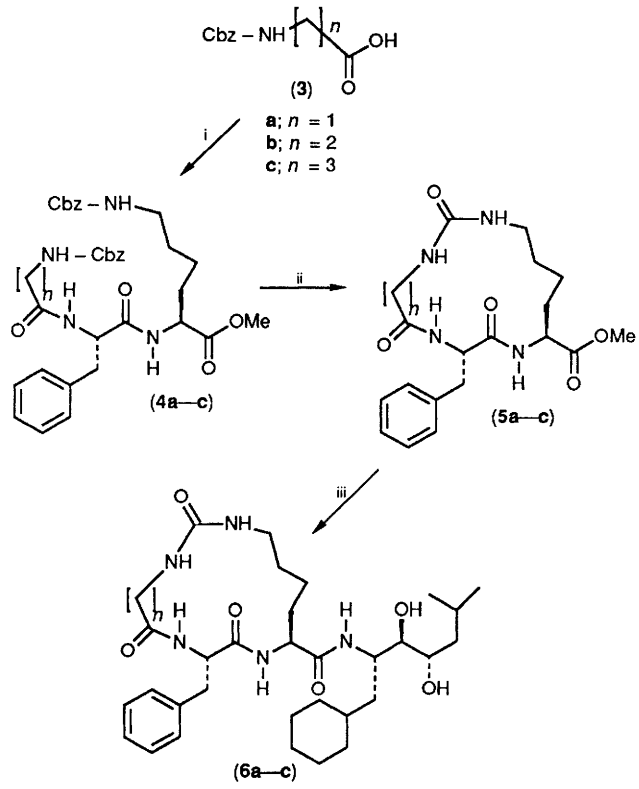


Figure 1. Schematic representation of a peptide bond that is cleaved by chymotrypsin, showing several important interactions of the substrate with the enzyme.

The syntheses of the target molecules (**6a**—**c**) were described using (**6a**) as an example. The syntheses of (**6b**) and (**6c**) followed the same procedures except replacing Cbz-glycine (**3a**) with Cbz-β-alanine (**3b**) and Cbz-γ-amino-butyric acid (**3c**) (Cbz = benzyloxycarbonyl). Coupling of Cbz-glycine (**3a**) with the dipeptide phenylalanine-ε-Cbz-lysine methyl ester using dicyclohexylcarbodiimide (DCC) provided (**4a**) (*n* = 1) in 85% yield. Hydrogenolysis of the Cbz-protecting groups of (**4a**) gave the diamino compound which was cyclized using phosgene in toluene under high dilution conditions to provide the novel cyclic peptide (**5a**) containing a metabolically stable urea linkage in 35% yield. Hydrolysis of the methyl ester with lithium hydroxide and coupling to the amino-glycol[4] fragment provided the renin inhibitor (**6a**) in 65% yield. The compounds† (**6a**—**c**) are potent inhibitors of human renin with IC_{50} of 1.8×10^{-7}, 1.2×10^{-8}, and 6.7×10^{-9} M respectively. More importantly, these three compounds are completely stable to degradation by the enzyme chymotrypsin ($t_{1/2}$ >24 h), with no detectable cleavage of the post-



Scheme 1. *Reagents*: i, DCC/phenylalanine-*N*-ε-*Z*-lysine methyl ester; ii, (a) H_2/Pd/C (b) $COCl_2/Et_3N$; iii, (a) LiOH (b) amino-glycol/DCC.

† All new compounds gave satisfactory spectral data and elemental analyses.

phenylalanine amide bond. The stability of the compounds may be due to their conformation in solution.

In conclusion, the synthesis of a series of potent human renin inhibitors containing cyclic peptides which are stable to degradation by chymotrypsin has been described.‡

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‡ Detailed conformational analysis of the cyclic peptides by Computer-Assisted Molecular Design techniques will be published elsewhere.

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