Novel Non-basic Bioisostere of Histidine synthesized from L-Aspartic Acid

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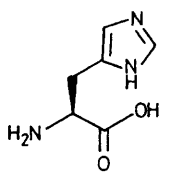
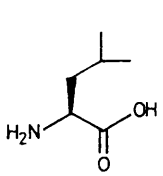
The incorporation of the novel bioisostere (**1c**) of histidine into a tripeptide led to a very potent and specific renin inhibitor.

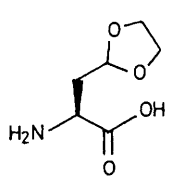
Two of the major design goals in the synthesis of biologically active peptides and related drugs, whether derived from naturally occurring compounds or not, are to achieve metabolic stability and enhanced oral bioavailability. We have reported[1] potent and specific inhibitors of renin that are tripeptides [(**7**) and (**8**) in Table 1] containing the natural amino acids histidine (**1a**) and leucine (**1b**). Recently tripeptide leupeptins possessing two hydrophobic leucine residues and an arginine residue were reported[2] to be excreted in bile; even larger basic oligopeptides like some of the peptide inhibitors of renin[3] lack oral activity owing to 'first-pass' clearance by hepatic biliary excretion. In order to investigate the possibility of reducing biliary excretion of renin inhibitors we attempted to substitute the histidine in (**7**) with other bioisosteric amino acids. We report here on the synthesis of amino acid (**1c**) (ADPA),† a novel non-basic bioisosteric[4] replacement for histidine, synthesized *via* L-aspartic acid.



(**1a**) Histidine



(**1b**) Leucine



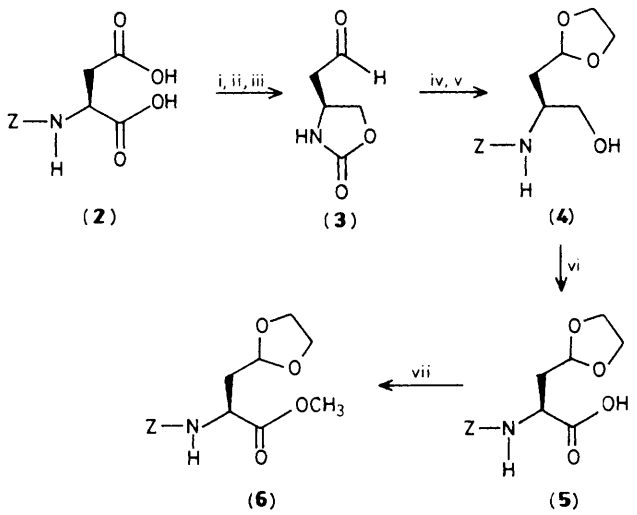
(**1c**) ADPA

† ADPA = (2*S*)-amino-3-(1,3-dioxolan-2-yl)propionic acid; ACHPA = (3*S*,4*S*)-4-amino-3-hydroxy-5-cyclohexylpentanoic acid.

Reaction of *N*-protected L-aspartic acid (**2**) with BH_3·tetrahydrofuran (THF) gave the corresponding diol which was treated with NaH in dimethylformamide (DMF) to give exclusively the 5-membered oxazolidinone alcohol. The primary alcohol was oxidized to the aldehyde (**3**) using pyridinium dichromate (PDC) in CH_2Cl_2 (70%, 3 steps). Reaction of (**3**) with ethylene glycol in benzene with catalytic amounts of toluene-*p*-sulphonic acid, followed by opening of the oxazolidinone ring with $Ba(OH)_2$ in dioxane/water and protection of the free amine with *N*-(benzyloxycarbonyloxy)-succinimide (Z-Suc), provided alcohol (**4**) (60%, 3 steps). Oxidation of the primary alcohol to the carboxylic acid using PDC[5] in DMF provided the protected amino acid (**5**) (70%, $[\alpha]_D^{21}$ −20.2°, *c* 1.0 in MeOH). The optical integrity of C-2 in

Table 1. Human renin and porcine pepsin inhibition by tripeptides containing histidine (**1a**), leucine (**1b**), and ADPA (**1c**).

Tripeptide	Human renin I.C.$_{50}$ 10^{-9} M	% Porcine pepsin at 10^{-5} M
(**7**) EtO_2C-Phe-His-ACHPA-(*S*)-2-methylbutylamine	3	24
(**8**) EtO_2C-Phe-Leu-ACHPA-(*S*)-2-methylbutylamine	2	65
(**9**) EtO_2C-Phe-ADPA-ACHPA-(*S*)-2-methylbutylamine	0.8	42



Scheme 1. Z = benzyloxycarbonyl; Reagents: i, BH_3·THF; ii, NaH/DMF; iii, PDC; iv, $HOCH_2CH_2OH/BF_3$·Et_2O; v, $Ba(OH)_2$ then Z-Suc; vi, PDC/DMF; vii, CH_2N_2.

(**5**) was determined in the following manner: (i) conversion of (**5**) into its methyl ester (**6**) by treatment with diazomethane in ether; (ii) deprotection and conversion of the free amino group into both the (+)- and (−)-Mosher amide.[6] The high field ^1H (300 MHz) and ^{19}F (339.6 MHz) n.m.r. spectra of the Mosher amides showed there was no detectable amount of (2*R*)-diastereoisomer in (**6**), demonstrating that (**5**) is of at least 95% enantiomeric excess (e.e.). Coupling of (**5**) to ACHPA-(*S*)-2-methylbutylamine† by the standard dicyclohexylcarbodiimide/2-hydroxybenzotriazole (DCC/HOBt) method followed by deprotection and coupling to ethoxycarbonyl-phenylalanine gave the tripeptide (**9**).

Comparison of (**9**) with analogous tripeptides (**7**) and (**8**) containing a histidine and a leucine residue respectively showed (Table 1) that tripeptide (**9**) containing the novel bioisostere (**1c**) of histidine synthesized *via* L-aspartic acid was the most potent renin inhibitor. Furthermore, it is important to note that (**9**) is as specific as (**7**) containing the histidine residue against human renin, showing some inhibition of another closely related aspartyl protease-porcine pepsin only at 10^{-5} M. The *in vivo* activity of compounds containing (**1c**) is under investigation.

Received, 11th June 1987; Com. 810

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