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β-LACTAM PEPTIDES AS POTENTIAL INHIBITORS OF THE HIV gp120-CD4 INTERACTION

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Abstract Peptides with an N-terminal clavulanic acid or 6-aminopenicillanic acid moiety were prepared as potential inhibitors of the binding interaction of HIV gp 120 with the CD4 receptor.

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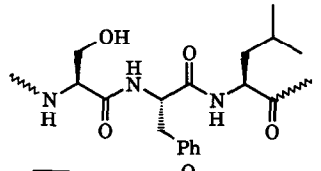
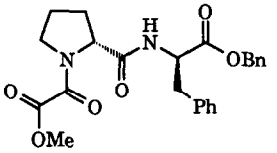
The ability of human immunodeficiency virus (HIV) to infect the majority of its susceptible cell types is dependent on the high affinity interaction of the envelope protein, gp120, with the cellular receptor CD4. This interaction has been intensively studied because of its potential as a target for anti-AIDS therapy.[1] Mutagenesis studies have identified the phenylalanine residue at position 43 of CD4 (see **1**) as a particularly important for binding.[2,3] In the crystal structure of the extracellular terminal two domains of CD4, the aromatic ring of this phenylalanine is clearly solvent-exposed and thus available for interaction with gp120.[4,5]

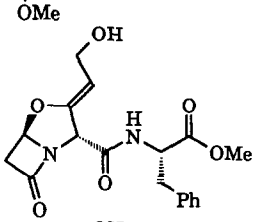
Recently, a series of phenylalanine-containing dipeptide derivatives termed CPFs (*eg* **2**) have been described as inhibitors of the gp 120-CD4 interaction.[6] The inhibitory activity claimed for these compounds is



1 residues 42 - 44 of CD4



2 CPF (DD isomer)



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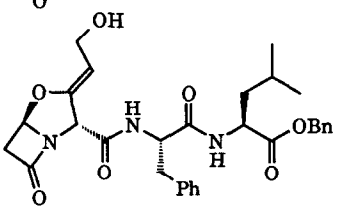

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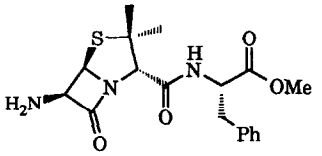

5

fairly weak (IC_{50} > 100μM) and is almost totally independent of the stereochemistry of both the phenylalanine and proline residues, although the DD-isomer **2** is marginally more active. However, when **2** is pre-incubated with gp120 and then washed out, the binding to CD4 is still disrupted suggesting the possibility of irreversible binding to gp120. A possible mechanism for this would be the selective acylation of a reactive moiety on the gp120 by the oxalyl ester of **2**. We considered the possibility of certain β-lactams performing a similar acylating function and on this basis have prepared some β-lactam containing peptides as potential inhibitors of the gp120-CD4 interaction.

The coupling of the β-lactams to phenylalanine methyl ester or phenylalanyl-leucyl benzyl ester were carried out by converting the free acid to an activated ester with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide and 1-hydroxybenzotriazole in DMF at 0°C either in the presence of, or with subsequent addition of, the amine component (liberated from its hydrochloride with diisopropylethylamine). Products were purified by silica gel chromatography or crystallisation. The coupling of clavulanic acid to afford **3** and **4** was performed without recourse to protecting the hydroxyl group. However, the amino group of 6-aminopenicillanic acid was protected in 80% yield by reaction with methoxytrityl chloride in the presence of both diethylamine and diisopropylethylamine in DMF. Deprotection of the coupled peptide to afford **5** was achieved in 65% yield by catalytic hydrogenolysis (10% Pd-C/MeOH/H_20).

Compounds **2** - **5** were tested for inhibition of the gp120-CD4 interaction in an ELISA based binding assay using recombinant gp120 and soluble CD4.[7] Whilst compound **2** had an IC_{50} of about 250μM in this assay system, compounds **3** - **5** showed no inhibition at concentrations up to 550, 350, and 250 μM respectively.

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References and notes

1. For recent reviews see: Capon D.J.; Ward R.H.W. *Annu. Rev. Immunol* **1991**, *9*, 649; Sweet R.W.; Truneh A.; Hendrickson W.A. *Current Opinion in Biotechnology* **1991**, *2*, 622.
2. Arthos J.; Deen K.C.; Chaikin M.A.; Fornwald J.A.; Sathe G.; Sattentau Q.J.; Clapham P.R.; Weiss R.A.; McDougal J.S.; Pietropaolo C.; Axel R.; Truneh A.; Maddon P.J.; Sweet R.W. *Cell* **1989**, *57*, 469.
3. Bowman M.R.; MacFerrin K.D.; Schreiber S.L.; Burakoff S.J. *Proc. Natl. Acad. Sci. USA* **1990**, *87*, 9052.
4. Wang J.; Yan Y.; Garrett T.P.J.; Liu J.; Rodgers D.W.; Garlick R.L.; Tarr G.E.; Husain Y.; Reinherz E.L.; Harrison S.C. *Nature* **1990**, *348*, 411.
5. Ryu S.-E.; Kwong P.D.; Truneh A.; Porter T.G.; Arthos J.; Rosenberg M.; Dai X.; Xuong N.; Axel R.; Sweet R.W.; Hendrickson W.A.; *Nature* **1990**, *348*, 418.
6. Finberg, R.W.; Diamond D.C.; Mitchell D.B.; Rosenstein Y.; Soman G.; Norman T.C.; Schreiber S.L.; Burakoff S.J. *Science* **1990**, *247*, 287.
7. Manuscript in preparation.