SYNTHESIS OF THE 2',3'-DIDEOXYNUCLEOSIDE DERIVATIVES OF THE SPECIFIC BINDING PEPTIDE PART OF CD4

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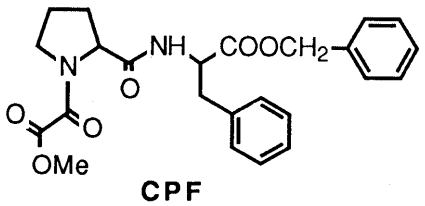
The 2',3'-dideoxynucleoside derivatives of the specific binding peptide part of CD4 to HIV envelope protein gp120 were synthesized.

KEYWORDS 2',3'-dideoxynucleoside derivative; glycoprotein CD4; envelope protein gp120; anti-HIV activity

Infection by human immunodeficiency virus type-1 (HIV-1) was found to be initiated when its envelope protein gp120 binds to the T-cell surface glycoprotein CD4 as its receptor.[1] The amino acid Ser^{42}-Ser^{49} region of the CD4 V1 domain was reported to be potent to bind to gp120.[2] Recently, Robert W. Finberg *et al.* have reported that *N*-carbomethoxycarbonyl-prolyl-phenylalanyl benzyl esters (CPFs) as the modified derivatives of the amino acid Ser^{42}-Phe^{43} region of the CD4 V1 domain blocked the binding of CD4 to gp120.[3]

-Ser^{42}-Phe-Leu-Thr-Lys-Gly-Pro-Ser^{49}-

Ser^{42}-Ser^{49} of CD4 V1 domain



CPF

The reverse transcriptase inhibitors such as the triphosphates of 3'-azido-3'-deoxythymidine (AZT) and the other 2',3'-dideoxynucleosides are currently the most effective chemotherapeutic agents for treatment of HIV infection.

Although AZT is at present the only drug used clinically for treatment of acquired immunodeficiency syndrome (AIDS), it displays severe bone-marrow toxicity with only short-term benefit[4], and resistant virus strains[5] are now emerging. From these facts we describe the synthesis of the AZT and 2',3'-dideoxynucleoside (ddN; *e.g.*, dideoxyuridine: ddU, dideoxycytidine: ddC, dideoxyinosine: ddI and dideoxyadenosine: ddA) (Fig. 1) derivatives having the peptide moiety to both bind specifically to the gp120 and inhibit the reverse transcriptase.

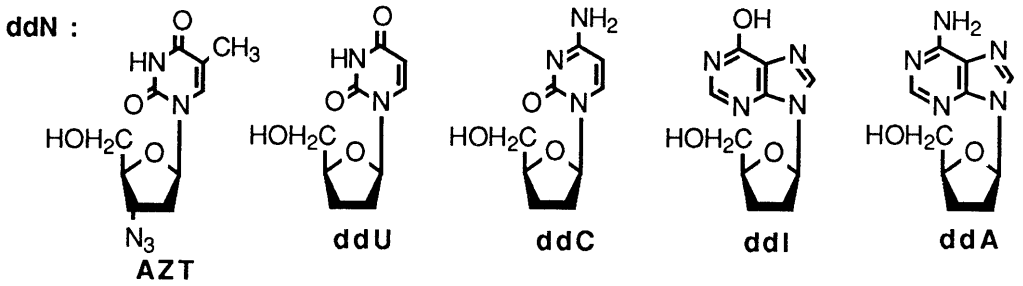


Fig. 1

We designed a structure constituting a link of oxalyl between ddNs and the specific binding peptide part of CD4.

The peptide part was synthesized from Boc-Pro-OH and H-D-Phe-OBzl•Tos-OH by diethyl phosphorocyanidate (DEPC)-triethylamine (TEA) coupling method.[6] The protected peptide Boc-Pro-D-Phe-OBzl was treated with HCl/AcOEt to give H-Pro-D-Phe-OBzl•HCl. Similarly, the octapeptide Ser^{42}-Ser^{49} of CD4 V1 domain was synthesized as shown in Chart 1.

Synthesis of the octapeptide Ser^{42}-Ser^{49}

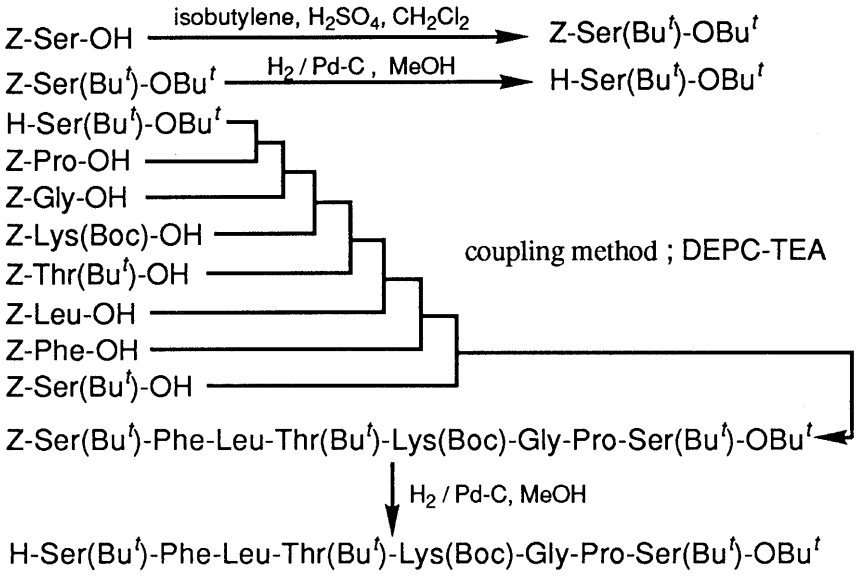


Chart 1

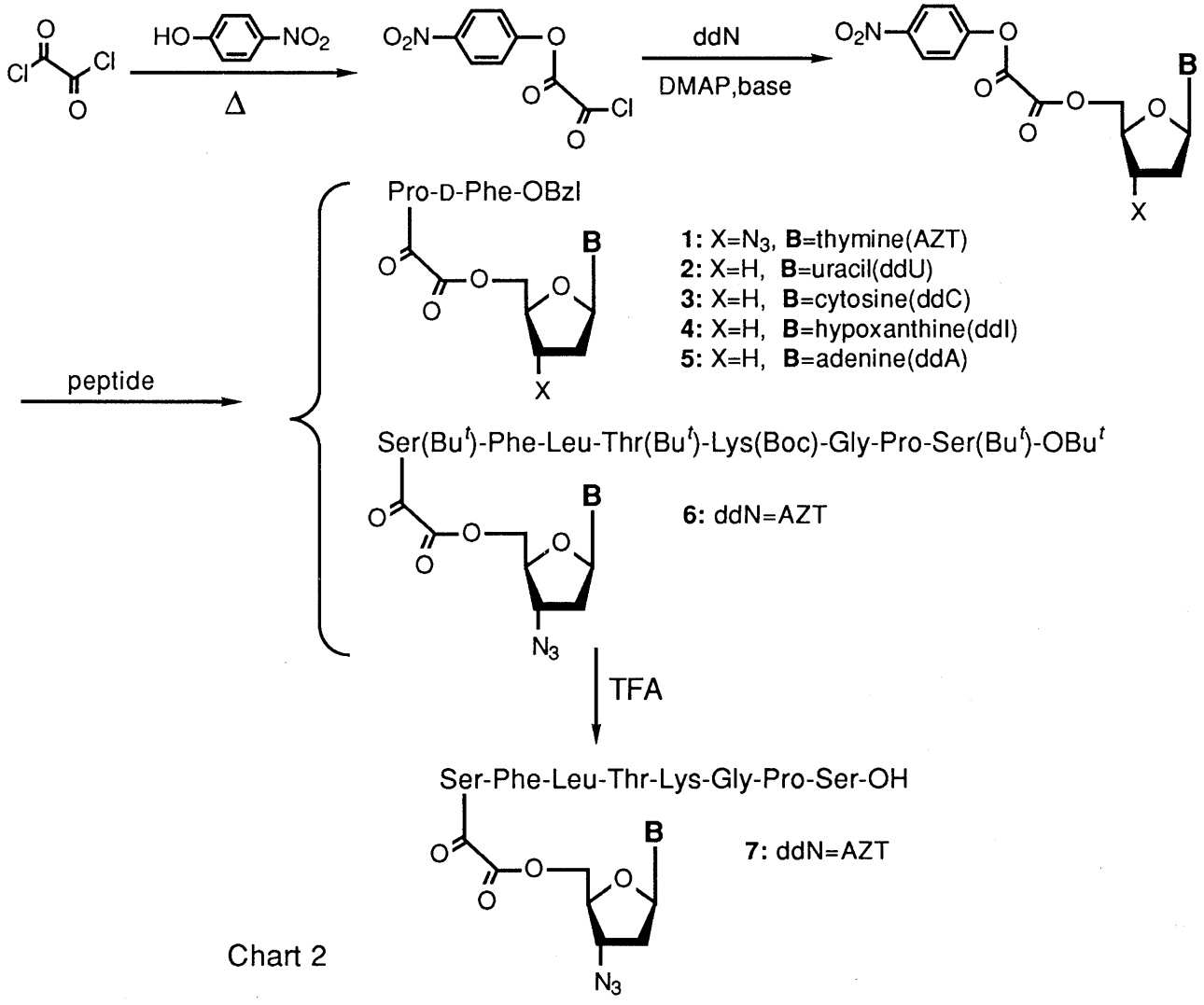


Chart 2

To obtain *p*-nitrophenyl chloroglyoxylate, *p*-nitrophenol was added to excess oxalyl chloride and the reaction mixture was refluxed for 16 h.[7] The purified chloroglyoxylate ester was treated with a variety of ddN in dry pyridine in the presence of 4-dimethylaminopyridine for 24-36 h at room temperature, followed by amidation with the corresponding peptide derivatives. Column chromatographic purification(SiO_2;$CHCl_3$:MeOH=10:1-6:1) of the reaction mixture afforded compounds(**1**-**6**) and succesive treatment of **6** with trifluoroacetic acid (TFA) gave the deprotected compound **7** (Chart 2).[8]

Preliminary examination of the biological activity revealed that compounds **1** and **3** show a significant inhibition of HIV infection.[9]

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8)**1**.(yield 32%) mp 75-78°C, $[\alpha]_D^{22}$ -38.2°(*c*=0.99;$CHCl_3$), FABMS(*m/z*) 674$(M+H)^+$, **2**.(yield 25%) mp 71-74°C, $[\alpha]_D^{22}$ -42.8°(*c*=0.31; $CHCl_3$), FABMS(*m/z*) 619$(M+H)^+$, **3**.(yield 12%) mp 72-76°C, $[\alpha]_D^{22}$ -9.3°(*c*=0.20;$CHCl_3$), FABMS(*m/z*) 618$(M+H)^+$, **4**.(yield 21%) mp 75-77°C, $[\alpha]_D^{22}$ -35.2° (*c*=0.20;$CHCl_3$), FABMS(*m/z*) 643$(M+H)^+$, **5**.(yield 24%) mp 72-75°C, $[\alpha]_D^{22}$ -8.5°(*c*=0.20;$CHCl_3$), FABMS (*m/z*) 642$(M+H)^+$, **6**.(yield 14%) mp 169-174°C, $[\alpha]_D^{22}$ -28.3°(*c*=0.28;$CHCl_3$), FABMS(*m/z*) 1482$(M+H)^+$, **7**.(yield 96%) mp 127-132°C, $[\alpha]_D^{22}$ -38.5°(*c*=0.28;$CHCl_3$:MeOH=1:1), FABMS(*m/z*) 1158$(M+H)^+$.

9)The detailed results of these biological activities will be published separately by Prof. Hiroo Hoshino *et.al.* (Gunma University).

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