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Synthesis and Anti-HIV Activity of New DABO Derivatives. E. Tramontano^, M.E. Marongiu^, M. Artico°, A. Mai°, S. Massa° and P. La Colla^. Depts. of ^Biologia Sperimentale, Università di Cagliari, and °Studi Farmaceutici, Università di Roma, Italy.

3,4-dihydro-2-alkoxy-6-benzyl-4-oxopyrimidines (DABOs) have been shown to be selective inhibitors of HIV-1 multiplication. The viral reverse transcriptase has been identified as the target of these compounds, which inhibit both the RNA- and DNA-dependent DNA polymerase associated activities.

We have synthesized new DABO derivatives characterized by either a 3,5-dimethylbenzyl ring at C6 or by both a 3,5-dimethylbenzyl at C6 and an alkylthio substituent at the C2 position.

Cytotoxicity and anti HIV-1 activity were evaluated by means of the MTT method.

The introduction of the 3,5-dimethylbenzyl ring led to compounds 10 fold more potent than the 6-benzyl counterparts. Moreover, the substitution of the 2-alkoxy for an alkylthio side chain led to a further 10 fold increase in potency.

In vitro assays with HIV-1 recombinant reverse transcriptase, performed using different template-primers, showed template-dependent potency of inhibition. The results of kinetic studies will be discussed.

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Anti-HIV-1 Activity of Phosphorothioate Oligonucleotides in Chronically and Acutely Infected Cells. M.E. Marongiu^, S. Corrias^, A. Cascino*, S. De Blase*, M. Santoro* and P. La Colla^. Depts. of ^Biologia Sperimentale, Università di Cagliari, and *Biochimica delle Macromolecole, Università di Napoli, Italy.

Phosphorothioate oligodeoxynucleotides, sense and antisense with respect to selected sequences of the HIV-1 gag, vif, vpr, rev and nef genes, were synthesized and tested for anti-HIV activity in chronically and acutely infected cells. As a random sequence, poly(dATG)19 was synthesized. The antiviral activity was evaluated by titration of infectious HIV-1 or by protection from the HIV-induced cytopathogenicity.

None of the oligos was cytotoxic at 20 uM. In chronically infected cells, rev (28mer) antisense was the most potent (ED90 = 0.1 uM), followed by gag (28mer) antisense (ED90 = 2 uM). Rev and gag sense, poly(dATG)19 and vif, vpr and nef (19mers) were ineffective.

In acutely infected MT4 cells, rev antisense was the most potent in preventing the HIV-1-induced cytopathogenicity (EC50 = 0.1 uM), followed by the other oligos (EC50 = 0.3 - 1 uM), poly(dATG)19 included.

Targets of the non sequence-specific anti-HIV activity of the phosphorotioate oligonucleotides are : a) the gp120-CD4 interaction; b) a step of the HIV multiplication cycle subsequent to provirus integration (as determined by time addition experiments).

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