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Biological Properties of Ro 31-8959

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A series of peptide derivatives containing a transition state mimetic of a Phe-Pro scissile bond has been evaluated as inhibitors of HIV proteinase and as potential therapeutic agents for the treatment of HIV infections. A novel assay, applicable to both HIV-1 and HIV-2 proteinases, was developed using a peptide substrate and quantifying cleavage by a colorimetric assay of N-terminal proline. In this assay the most active compound, Ro 31-8959, has a Ki value close to 0.1nM against both HIV-1 and HIV-2 proteinases. Ro 31-8959 also inhibits HIV gag and gag-pol cleavage in cell free and whole cell systems and has potent antiviral activity. It has little effect on human aspartic proteinases or on representatives of other proteinase classes.

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Gag and Pol Antisense Oligodeoxynucleotides as Inhibitors of HIV 1.

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Sequences from the Gag-Pol region of the HTLV III RF strain of HIV 1 were chosen as targets for antisense oligodeoxynucleotides; both normal (O-oligos) and phosphorothioate analogues (S-oligos) were synthesised. These included: overlapping sequences from the junction of the P18/P24 transcript, the Gag-Pol frame shift sequence, the junction sequence between the protease and RT transcript and a poly S-dC22 control. Sequences ranging from 13 to 24 deoxynucleotides in length were tested in both acutely and chronically infected lymphoblastoid cells. O-oligos were inactive. All S-oligos showed activity, in acutely infected cells, which was chain length dependent. But in chronically infected cells S-oligos were dependent on the sequence specificity of the antisense molecule. These results are consistent with previous in vitro studies (Matsukura et al., PNAS, 84, 7706, 1987 and PNAS, 86, 4244, 1989; S Agrawal, PNAS, 86, 7790) which demonstrate that antisense oligodeoxynucleotides have several modes of action.