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HIV TAT Inhibitor

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The tat gene product of HIV is required for viral replication. It is a strong positive regulator of viral transcription and possibly also functions to enhance the translation of viral mRNA. Tat is therefore a novel target for antiviral therapy of HIV infection. An inhibitor of tat would have the potential to arrest the virus in the dormant state. Ro 5-3335, identified with a sensitive, high-flux screen, suppresses gene expression controlled by the HIV LTR promoter. Studies with mutant promoters and purified recombinant tat showed that the compound inhibited tat-specific transcriptional transactivation. Consistent with its mode of action, Ro 5-3335 inhibits HIV replication at the level of viral RNA synthesis and is effective in acutely- as well as chronically-infected cells, a characteristic unique among anti-HIV agents. The compound is equally effective against AZT-sensitive and -resistant viral isolates from AZT-treated patients, and is synergistic with AZT.

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GAG AND REV ANTISENSE OLIGODEOXYNUCLEOTIDES AS INHIBITORS OF HIV 1.

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Antisense S-oligodeoxynucleotides from the gag and rev sequences of HIV-1 were compared for their antiviral activity in both acutely and chronically infected cells. The activity of these sequences, which ranged from 13 -28 deoxynucleotides in length, were compared with 22mer and 28mer S-oligodeoxycytidylic acid controls. S- oligos in C8166 cells acutely infected with the RF strain of HIV 1 had an EC50 in the 0.5 -5 μM range. These results show that the activity of S-oligos in acutely infected cells are chain length dependent. To study the mechanism of action, the time of addition of S-oligos post infection was delayed for up to 24 hours and the results compared to those obtained with ddC and TIBO derivatives. It was found that addition could be postponed for 24 hours to retain significant antiviral activity, whereas ddC and TIBO derivatives lost activity after 5-10 hours delayed addition. This result is consistent with the S-oligos having several modes of action which may be the inhibition of reverse transcriptase and binding to cell membranes. Activity of S-oligos in chronically infected cells has shown some variation in H9 cells chronically infected with HIV-1 (RF): both the antisense S-oligos and the S-oligodeoxycytidylic acid controls have shown activity in the 1-10 μM range. the mode of action of these compounds in acutely and chronically infected cells will be discussed.