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Report by the Research Team of G. Folkers*  

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Discovery of Indinavir and Efavirenz, New Therapeutic Agents for AIDS

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For the treatment of HIV infection, two enzymes are of major interest: The HIV-1 Protease (PR) and the Reverse-Transcriptase (RT).

The HIV-Protease, an aspartic-acid protease active as a dimer, is responsible for the cleavage of polypeptides assembled at the cell membrane. The inhibition of the protease-mediated cleavage of the viral precursor polyproteins results in the production of noninfectious progeny viral particles. The development of Indinavir started with screening a collection of renin inhibitors. A seven-amino-acid analog 1 which contains the hydroxyethylene tran-
prevents the spread of the virus. Different nucleoside inhibitors like AZT, ddI, ddC, d4T and 3TC are already known, but new non-nucleoside inhibitors (NNRTI) are developed to decrease the cytotoxicity and to improve the selectivity of the viral polymerases vs. mammalian ones.

The identification of new lead compounds was accomplished using an assay measuring the incorporation of ^3H-dGTP into rCdG. The screening was carried out with the Merck sample collection containing about 10^6 compounds. Initial lead compounds from the pyridinone class showed a rapid drop in vRNA but also a rapid emergence of resistant viruses. Further lead structures were thiourea compounds with IC_{50}(rCdG) = 60 nM (3). The introduction of a smaller alkyl group at C(4) improved the activity to IC_{50}(rCdG) = 8 nM. The problem of these compounds was the reactivity and the toxicity. Their oxoanalogues with a cyclopropyl group at C(4) and different alkyl substituents were synthesized (4).

All compounds exhibited a low bioavailability, except the compound with a 4-acetylene functionality (IC_{50}(rCdG) = 30 nM). By incorporating an aryl group onto the end of the 4-acetylene functionality, the requirement for a metabolically labile 3-methyl group on the dihydroquinazoline nucleus was eliminated. The demethylated compound showed approximately the same activity and an increase in bioavailability.

To prevent metabolic methylation, the nitrogen was replaced by an oxygen giving benzoxazinone derivatives. A member of this class, compound L-743,726 (Efavirenz, 5), was found to be a potent inhibitor of the wild-type RT (K_I = 2.93 nM, IC_{50} = 1.5 nM). This compound was also found to be capable of inhibiting a panel of NNRTI-resistant mutant viruses with IC_{50} = 1.5 μM.

In the triple therapy (EFV+ZDV+3TC), statistically significant differences were observed vs. standard triple therapy (IDV+ZDV+3TC) in terms of higher percentage of patients with lower levels than 400 RNA copies per ml during the first 24 weeks. The mean change of CD4 counts from baseline at 36 weeks was approximately the same as in standard triple therapy.

The second enzyme of interest is the HIV-1 reverse transcriptase (RT) which consists of the two subunits p66 and p51 and acts as polymerase and RNase responsible for the transcription of viral ssRNA to dsDNA. The inhibition of this enzyme prevents the spread of the virus. Different nucleoside inhibitors like AZT, ddI, ddC, d4T and 3TC are already known, but new non-nucleoside inhibitors (NNRTI) are developed to decrease the cytotoxicity and to improve the selectivity of the viral polymerases vs. mammalian ones.

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