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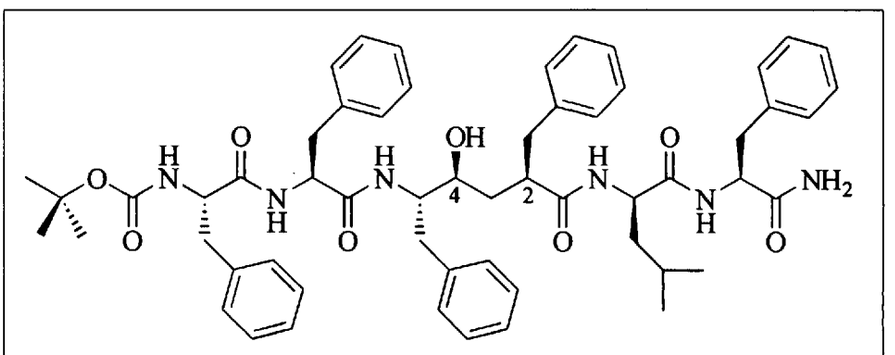
For the treatment of HIV infection, two enzymes are of major interest: The HIV-1 Protease (PR) and the Reverse-Transcriptase (RT).

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-



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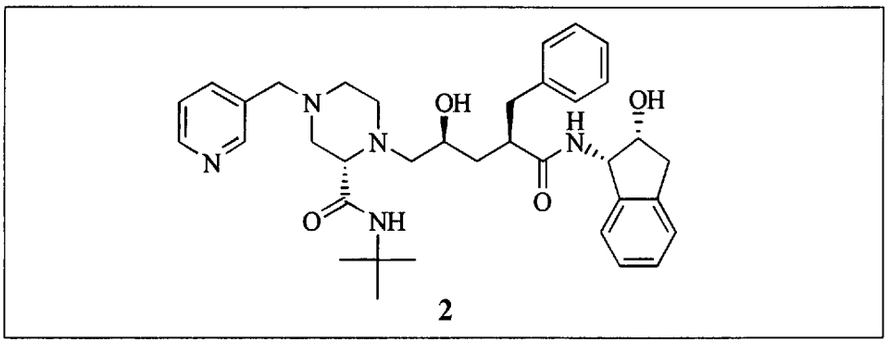

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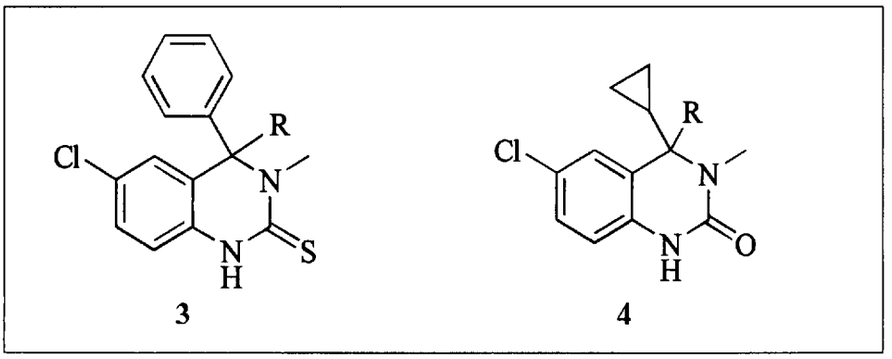

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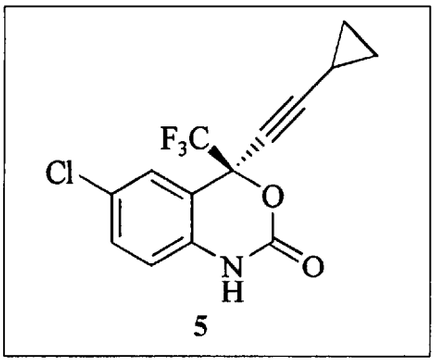

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sition-state isostere was identified as a potent inhibitor of PR:

The potency was characterized by measuring IC_{50} and CIC_{95} values. This compound served as starting-point for different modifications. The binding to the protease is stereoselective and requires the absolute configuration at the hydroxy-C(4) and P_1'-substituted C(2) C-atoms to be (*S*) and (*R*), respectively. The deletion of the *N*-terminal two amino-acid residues (–Phe-Phe) led to a more potent inhibitor of PR which had lost its activity against renin. The replacement of the *C*-terminal leucylphenylalanylamide dipeptide by a benzyl amide afforded an inhibitor retaining inhibitory activity against PR. The benefit of this approach was the reduction of the molecular weight and the elimination of several peptide bonds diminishing the potential for recognition by degradative proteases *in vivo*. The replacement of the benzylamide by an indane moiety increased the activity to IC_{50} = 26 nM. Additional introduction of a hydroxy group *cis* to the amino functionality increased the activity to a subnanomolar range (IC_{50} = 0.3 nM). To improve the water solubility, different compounds were designed by molecular modeling. The introduction of a morpholinoethoxy group in the P_1' phenyl position gave an increase of the solubility but a lower activity (IC_{50} = 0.45 nM). Due to the low bioavailability of the new compound (only 3–5% in dogs and rats), new modifications were developed. The replacement of the Boc-Phe portion by a decahydroisoquinolineamine and the exploration of further isosteres of this decahydroisoquinoline group finally led to a N^4-substituted piperazine compound (*Indinavir*, **2**) with good oral bioavailability in three different animal species.

The new potent protease inhibitor was tested in combination with other antiretroviral drugs and showed a profound and sustained suppression of HIV replication. The decrease in HIV RNA over the first 24 weeks was greater in the three-drug group than in the other groups. The increase in CD4-cell counts over the first 24 weeks was greater in the two groups receiving *Indinavir* than in the *Zidovudine-Lamivudine* group. The changes in the viral load and the CD4-cell count persisted for up to 52 weeks.

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, d_4T 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 ^{3}H-dGTP into rCdG. The screening was carried out with the *Merck* sample collection containing about 10^5 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 oxo-analogues 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 dihydroquinazolinone 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, CIC_{95} = 1.5 nM). This compound was also found to be capable of inhibiting a panel of NNRTI-resistant mutant viruses with $CIC_{95} \leq 1.5$ 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 vRNA 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.