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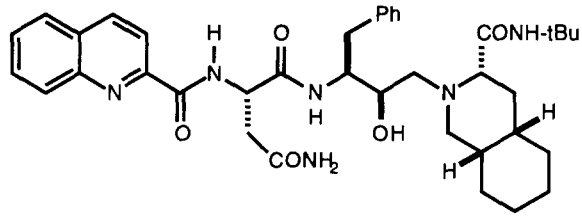
NEW DRUGS—REPORTS OF NEW DRUGS RECENTLY APPROVED BY THE FDA

Saquinavir



Structure
$C_{38}H_{50}N_6O_5$

N-*tert*-butyl-decahydro-2-(2(*R*)-hydroxy-4-phenyl-3-(*S*)-((*N*-(2-quinolylcarbonyl)-L-asparaginyl)amino)butyl)-4a*S*,8a*S*-isoquinoline-3(*S*)-caboxamide
[CAS 127779-20-8]

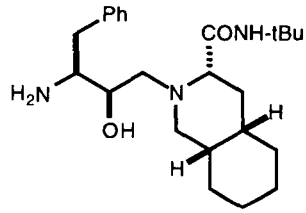
Supply: Methanesulfonate $C_{38}H_{50}N_6O_5 \cdot CH_4O_3S$.

Invirase, Ro-31-8959/003, Ro 318959

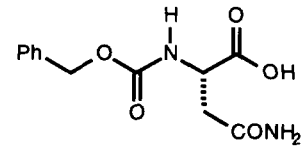
Mechanism of action: Saquinavir is a synthetic peptide-like substrate analogue that inhibits the activity of HIV protease and prevents the cleavage of viral polyproteins.

Therapeutic category: Antiviral agent.

Synthesis: Several new routes for the large scale synthesis of saquinavir have been demonstrated. Saquinavir can be synthesized by the condensation of two key intermediates, A and B.



A



B

Summary: Saquinavir is active against HIV-1 and HIV-2 protease in both cell-free and whole cell systems. Saquinavir inhibits the breakdown of the viral protein precursor p55 and prevents viron maturation. No cytotoxicity has been observed with this compound. The IC_{50} values were in the range of 1–30 nM. In cell culture saquinavir demonstrated additive to synergistic effects against HIV in double and triple combination regimens with reverse transcriptase inhibitors zidovudine (ZDV), zalcitabine (ddC), and didanosine (ddI), without enhanced cytotoxicity. The absolute bioavailability is around 4%. The low bioavailability is thought to be due to a combination of incomplete absorption and extensive first-pass metabolism. HIV isolates with reduced susceptibility to saquinavir have been selected in vitro. Genotypic analyses of these isolates showed substitution mutations in the HIV protease at amino acid position 48

(Gly to Val) and 90 (Leu to Met). Phenotypic and genotypic changes in HIV isolates from patients treated with saquinavir were also monitored in phase I/II clinical trials. However, the clinical relevance of phenotypic and genotypic changes associated with saquinavir therapy has not been established. The recommended dose of Invirase in combination with a nucleoside analogue is three 200 mg capsules three times daily (1.8 g/day) taken within 2 h after a full meal. Invirase should be used only in combination with an active antiretroviral nucleoside analogue regimen.

Manufacturer: F. Hoffmann-La Roche & Co., Ltd. (Switzerland) or Roche Laboratories Inc. (U.S.A.)

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