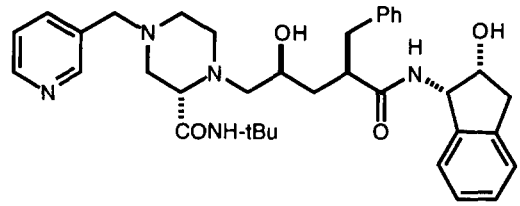
Pergamon

Bioorganic & Medicinal Chemistry, Vol. 5, No. 3, pp 463–464, 1997

PII: S0968-0896(96)00261-1
0968-0896/97 $17.00 + 0.00

New Drugs—Reports of New Drugs Recently Approved by the FDA

Indinavir



Structure
$C_{36}H_{47}N_5O_4$

(1(1*S*,2*R*),5(*S*)-2,3,5-Trideoxy-*N*-(2,3-dihydro-2-hydroxy-1*H*-inden-1-yl)-5-(2-(((1,1-dimethylethyl)amino)carbonyl)-4-(3-pyridinylmethyl)-1-piperazinyl)-2-(phenylmethl)-D-erythro-pentonamide
[CAS 150378-17-9]

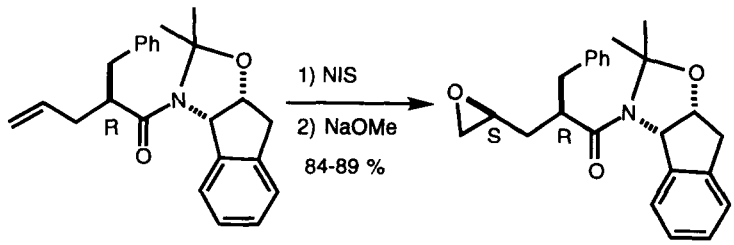
Supply: Sulfate, a white to off-white, hygroscopic crystalline powder.

Crixivan, MK-639, L-735,524

Mechanism of action: Indinavir binds to the HIV protease active site and inhibits the activity of the enzyme. This inhibition prevents cleavage of the viral polyproteins resulting in the formation of immature noninfectious viral particles.

Therapeutic category: Antiviral agents.

Synthesis: The discovery of an efficient syn-epoxidation of 2-substituted-4-enamides to the corresponding epoxy-amides provided an efficient route to indinavir.



Summary: The IC_{95} (95% inhibitory concentration) of indinavir was in the range of 25–100 nM. In drug combination studies with the nucleoside analogues zidovudine and didanosine, as well as with an investigational non-nucleoside (L-697,661), indinavir showed synergistic activity in cell culture. Viral resistance was correlated with the accumulation of mutations that resulted in the expression of amino acid substitutions in the viral protease. Eleven amino acid residue positions have been identified. Indinavir was rapidly absorbed in the fasted state. Cross-resistance was noted between indinavir and the protease inhibitor ritonavir. Varying degrees of cross-resistance have been observed between indinavir and other HIV-protease inhibitors. Seven metabolites have been identified, one glucuronide conjugate and six oxidation metabolites. In vitro studies indicate that cytochrome P-450 3A4 (CRY3A4) is the major enzyme responsible for formation of the oxidative metabolites. Indinavir has been studied in phase III clinical trials as

a monotherapy (dose-escalation) and in combination with zidovudine and with zidovudine + didanosine. The recommended dosage of Crixivan is 800 mg (two 400 mg capsules) orally every 8 h. The dosage is the same whether Crixivan is used alone or in combination with other antiretroviral agents. In an analysis of early clinical trials for safety, nephrolithiasis was the only clinically significant ADR.

Manufacturer: Abbott Laboratories (U.S.A.)

Yukari Ohta* and Ichiro Shinkai
Banyu Clinical Research
2-9-3 Shimomeguro
Meguro-ku
Tokyo
Japan