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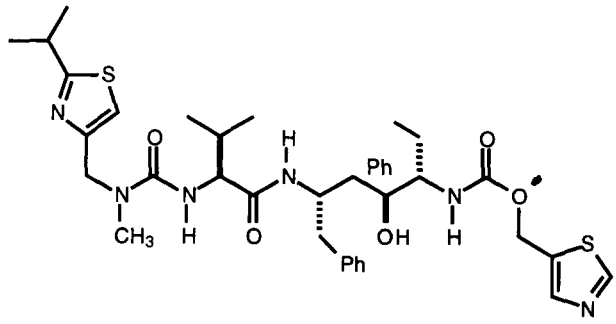
NEW DRUGS—REPORTS OF NEW DRUGS RECENTLY APPROVED BY THE FDA

Ritonavir



Structure
$C_{37}H_{48}N_6O_5S_2$

10-Hydroxy-2-methyl-5-(1-methylethyl)-1-(2-(1-methylethyl)-4-thiazolyl)-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid, 5-thiazolylmethylester, (5*S*-(5*R**,8*R**,10*R**,11*R**))
[CAS 155213-67-5]

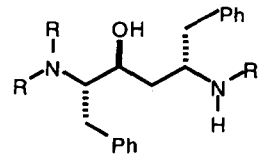
Supply: A white-to-light tan powder

Norvir, A-84538, ABT-538

Mechanism of action: Ritonavir is a peptidomimetic inhibitor of both the HIV-1 and HIV-2 proteases. Inhibition of HIV protease renders the enzyme incapable of processing the Gag-pol polyprotein precursor which leads to production of noninfectious immature HIV particles.

Therapeutic category: Antiviral agent.

Synthesis: Ritonavir can be synthesized via the key intermediate 2,5-diamino-3-hydroxyhexane (US 5,543,551 and US 5,543,552).



Summary: The concentration of drug that inhibits 50% of viral replication (EC_{50}) ranged from 3.8 to 153 nM depending upon the HIV-1 isolate and the cells employed. The average EC_{50} for low passage clinical isolates was 22 nM. In a 1090-patient study, 1.2 g of the drug used concomitantly with existing nucleoside therapy, produced a significant decrease in mean viral RNA levels of placebo and an increase in average change of CD4 count over the first 16 weeks. After seven months the mortality rate was 4.8% for ritonavir patients and 8.4% for placebo. Ritonavir demonstrated additive effects against HIV-1 in combination with either zidovudine (ZDV) or didanosine (ddI).

Genotypic analysis of HIV-1 isolates with reduced susceptibility to ritonavir showed mutations in the HIV protease gene at amino acid positions 84 (Ile to Val), 82 (Val to Phe), 71 (Ala to Val), and 46 (Met to Ile). Phenotypic and genotypic changes in HIV isolates from selected patients treated with ritonavir were monitored in phase I/II trials over a period of 3–32 weeks. Mutation appeared to occur in a stepwise and ordered fashion. The potential for HIV cross-resistance between protease inhibitors has not been fully explored. The absolute bioavailability of ritonavir has not been determined. After a 600 mg dose of oral solution, peak concentrations of ritonavir were achieved approximately 2 and 4 h after dosing under fasting and nonfasting conditions, respectively. The isopropylthiazole oxidation metabolite (M-2) is the major metabolite. Studies utilizing human liver microsome have demonstrated that cytochrome P450 3A (CYP3A) is the major isoform involved in ritonavir metabolism, although CYP2D6 also contributes to the formation of M-2. Agents that increase CYP3A activity would be expected to increase the clearance of ritonavir resulting in decrease of ritonavir plasma concentration. Ritonavir can produce a large increase in plasma concentrations of certain highly metabolized drugs. Ritonavir prevents fast metabolism of saquinavir allowing increased blood levels. Addition of saquinavir is not expected to accelerate resistance to ritonavir due to the distinct mutation profiles of both drugs. Norvir capsules are available for oral administration in a strength of 100 mg ritonavir. Norvir oral solution is also available for oral administration as 80 mg/mL of ritonavir in a flavored vehicle.

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

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