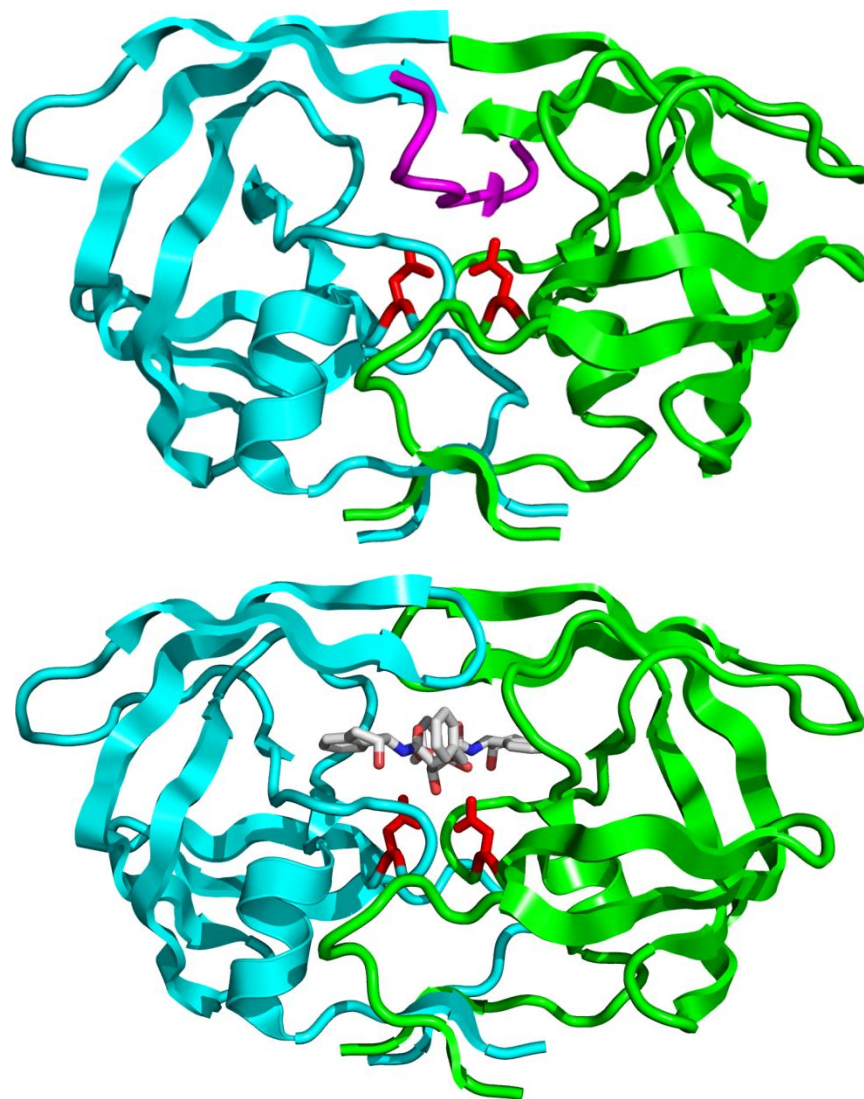


from *Chem Rev* 1997, 97, 1359.



Pepstatin binding in HIV protease

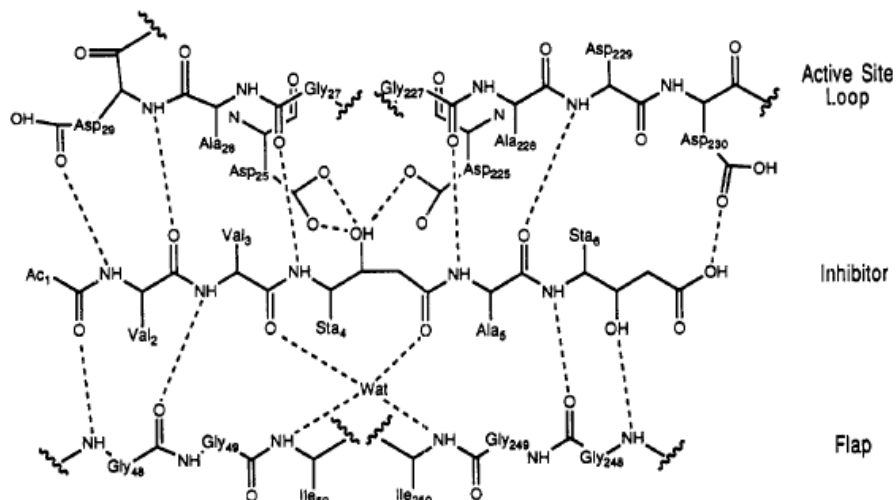


Figure 3. Hydrogen bonds between acetyl pepstatin and HIV-1 protease. The residues are labeled at the C- β position (C- α for glycine). The residues labeled 25–50 are from monomer A; those labeled 225–250 are from monomer B; and those labeled 1–6 are associated with acetyl pepstatin.

from J. R. Huff, *J. Med. Chem.* **1991**, 34(8), 2305-2314.

Roche's development of the first HIV protease inhibitor

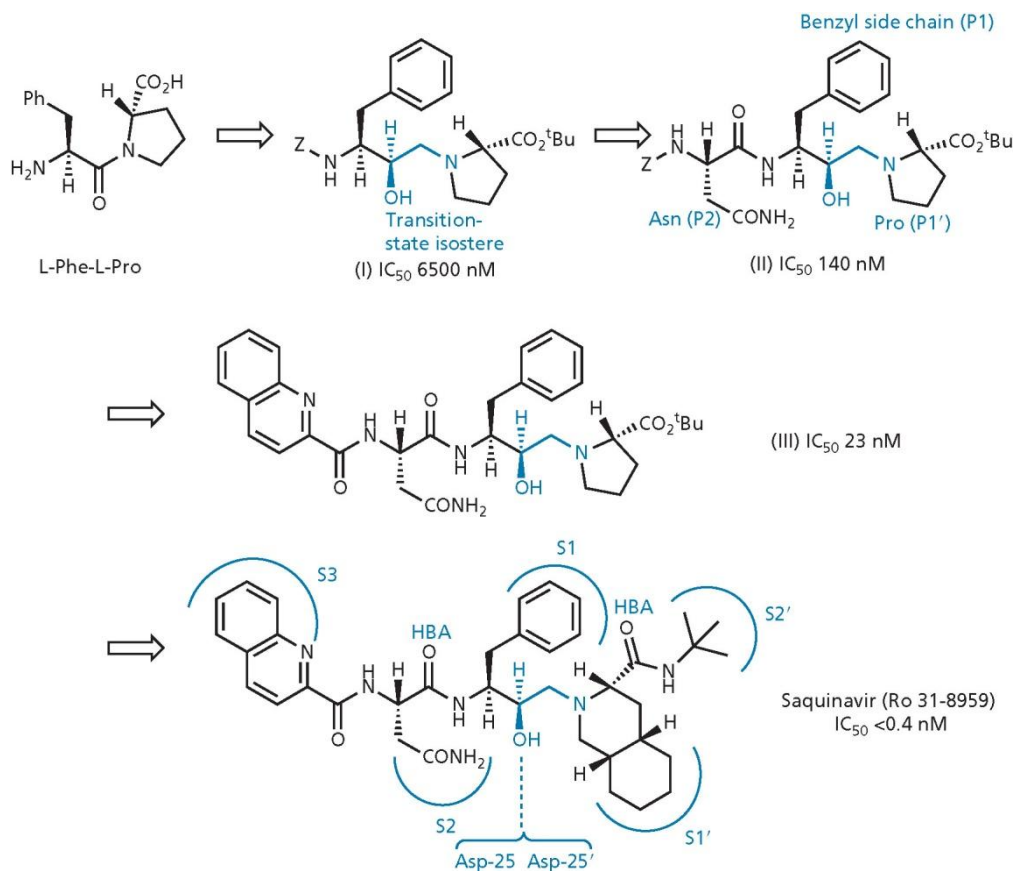
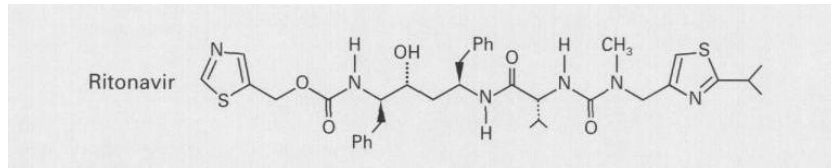
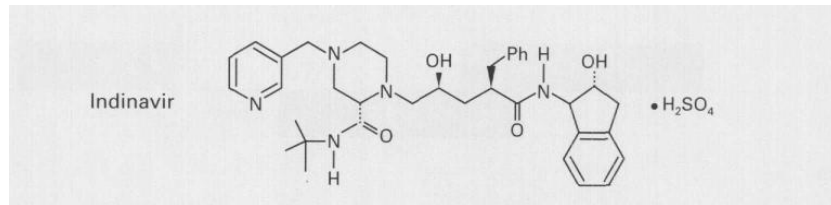


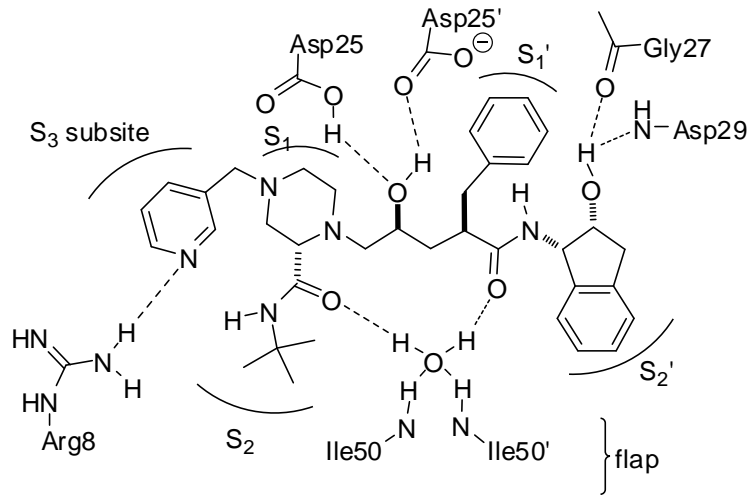
fig. 20.22 in Patrick



-ritonavir (Norvir), Abbott, 1996 (7th anti-retroviral drug approved)

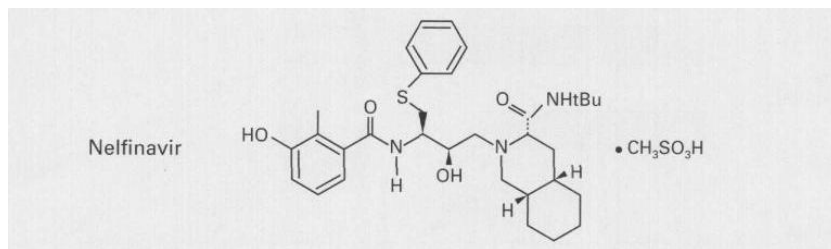


-indinavir (Crixivan), Merck, 1996

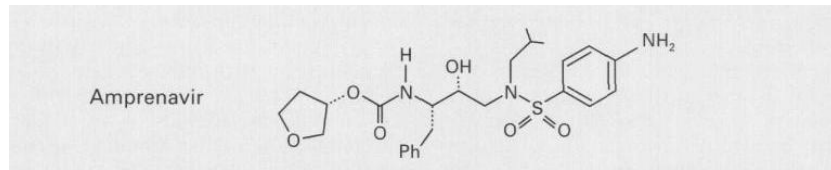


Crixivan's Interactions in HIV-2 proteases active site

Chen et al. (Merck) *JBC* **1994**, 269, 26344-26348.



-nelfinavir (Viracept), Agouron, 1997



-aprenavir (Agenerase), Vertex/Glaxo, 1999

TABLE 1. PHARMACOKINETICS OF APPROVED HIV-PROTEASE INHIBITORS.*

DRUG	DOSE†	APPROXIMATE ORAL BIO- AVAILABILITY	EFFECT OF FOOD‡	C _{max}	T _{max}	T _{1/2}	VARIABILITY§	PROTEIN BINDING	V _d	CSF CONCENTRATION¶	CLEARANCE (ROUTE)	P-450	
												INDUC- TION	INHIBI- TION
	mg	%	%	μg/ml	hr	hr	%	%	liters/kg	%	%		
Indinavir	800 every 8 hr	60–65	-77	7.7	0.8	1.8	22–47	60–65	NR	2.2–76**	88–90 (hepatic)	No	Yes
Nelfinavir	750 three times a day	>78	+200 to +300	3.0–4.0	2.0–4.0	3.5–5.0	NR	>98	2.0–7.0	NR	>78 (hepatic)	Yes	Yes
Ritonavir	600 twice a day	66–75††	-7 (liquid); +15 (capsules)††	11.2	2.0–4.0	3.0–5.0	30–36	98–99	0.4	1††	>95 (hepatic)	Yes	Yes
Saquinavir	600 three times a day	<4	+670	0.2	NR	NR	46–84	98	10.0	<1	>97 (hepatic)	No	No††

*Data are mean values and ranges in adults without hepatic or renal dysfunction, as reported by Merck (for indinavir),²¹ Agouron Pharmaceuticals (for nelfinavir),²² Abbott Laboratories (for ritonavir),²³ and Roche Laboratories (for the Invirase formulation of saquinavir).²⁴ C_{max} denotes maximal concentration during a dosing interval, T_{max} time to the maximal concentration, T_{1/2} half-life of the principal elimination (β) phase, V_d volume of distribution, CSF cerebrospinal fluid, P-450 cytochrome P-450 drug-metabolizing enzymes (with "induction" denoting a significant increase and "inhibition" a significant decrease in the metabolism of other P-450 substrates), and NR not reported.

†Recommended doses and regimens are listed.

‡The effect of food is expressed as the change in the area under the plasma-concentration–time curve after a standard (high-fat) breakfast as compared with the area under the curve during fasting.

§Variability is expressed as the coefficient of variation (the standard deviation divided by the mean) for the area under the curve during a dosing interval.

¶The values shown are the ratio of the CSF concentration to the simultaneous plasma concentration.

||Lighter meals (toast and coffee or corn flakes with skim milk) have no significant effect on the area under the curve.

**Data are from Collier et al.²⁵

††Data are on file at Abbott Laboratories.

‡‡In vitro studies show that saquinavir can act as a P-450 inhibitor at higher concentrations than those usually achieved with the Invirase formulation.²⁶

from *New England Journal of Medicine* 1998, 338(18), 1281-1293.