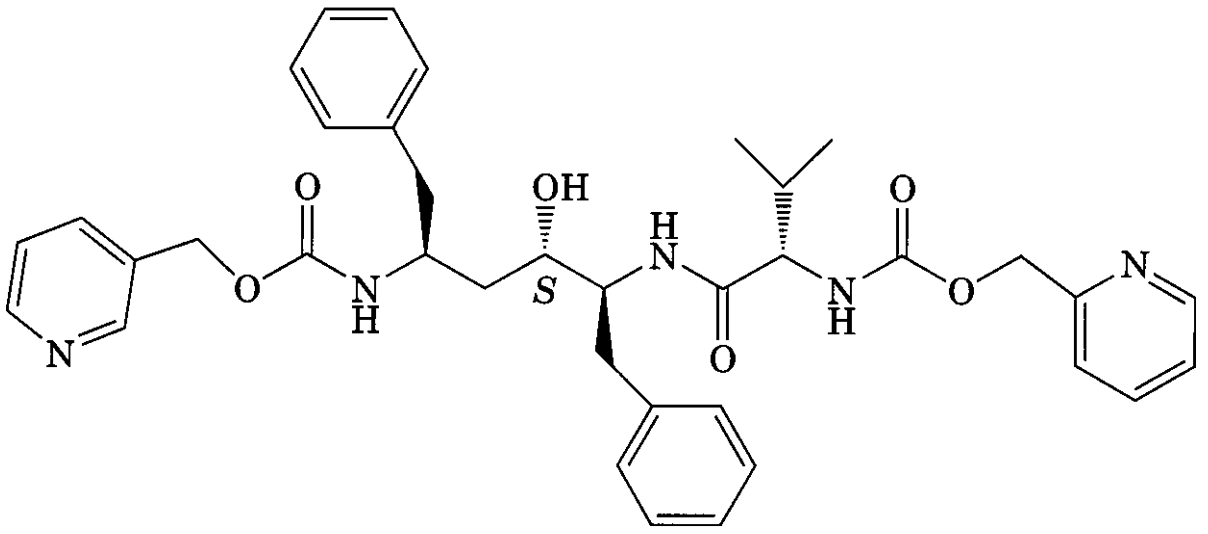
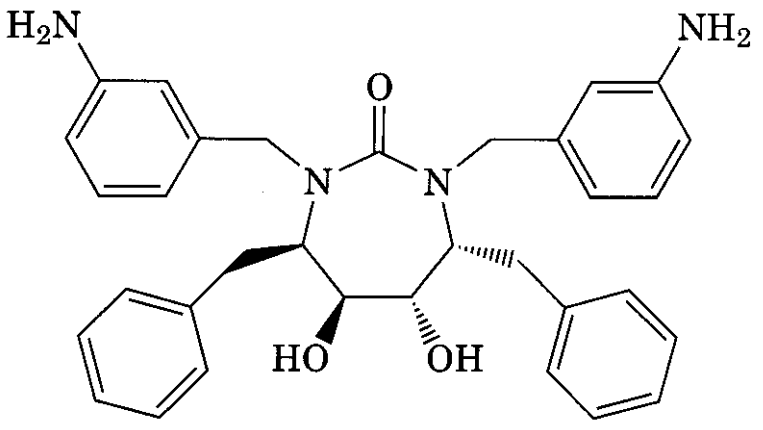


(34) A-80987

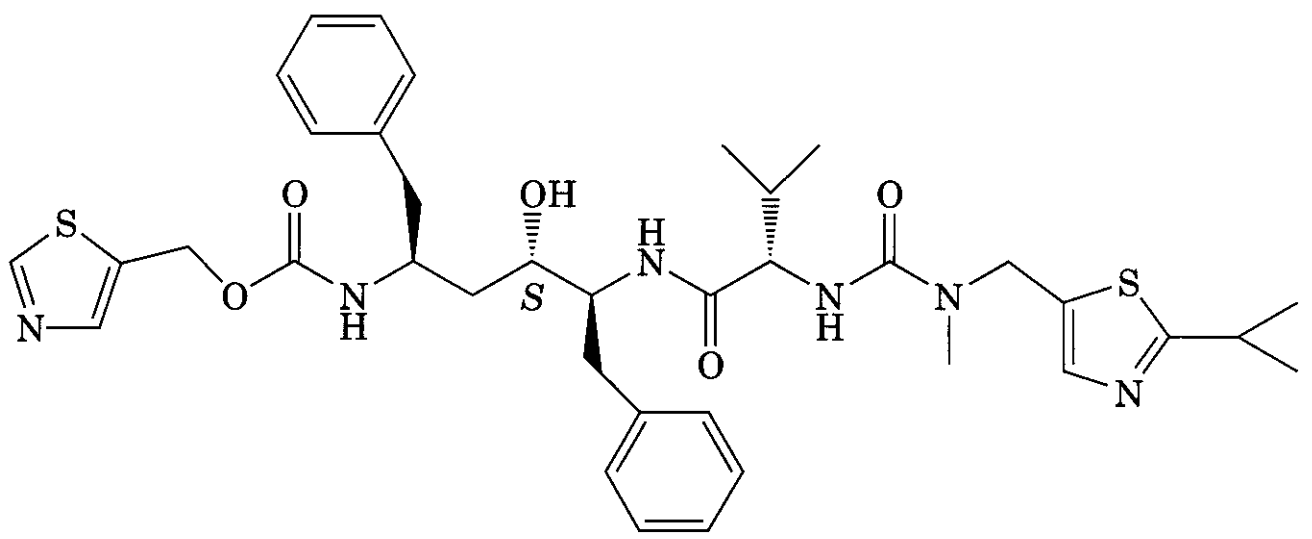
contact. Thus the cost of desolvating the second inhibitor hydroxyl upon binding is not compensated by strongly favorable interactions in the complex (8). This led to the deletion of the second hydroxyl, as seen in compound **(34)**, another compound in this program at Abbott. Further structural modifications, to enhance solubility and metabolic stability, were guided by the fact that the "ends" of the protease-bound inhibitors were relatively solvent exposed and made fewer contacts with the enzyme (102). Deletion of a valine residue (33→34) gave a smaller compound, presumably aiding solubility and absorption. The eventual product of this program was ritonavir (**35**, A-84538, ABT-538, or Norvir), which has been successfully launched.

Another C2 symmetric HIV-P inhibitor, discovered at Dupont Merck is compound (36) (DMP-450). This was one of a series of cyclic ureas designed to interact with both the aspartyl carboxylates and the Ile50 and Ile50′ backbone amides that hydrogen bond with the flap water (103). The compounds interacted with HIV-P in a highly symmetrical fashion, as they had been designed to do, with the urea oxygen replacing the flap water. Compound (36) was licensed to Triangle Pharmaceuticals, and the mesylate advanced into Phase I clinical trials. Its future is uncertain after the trials were put on hold because of animal toxicity (http://www.tripharm.com/dmp45O.html).



(36)

One of problems common to many of the HIV-P inhibitors already discussed is their



(35) ritonavir