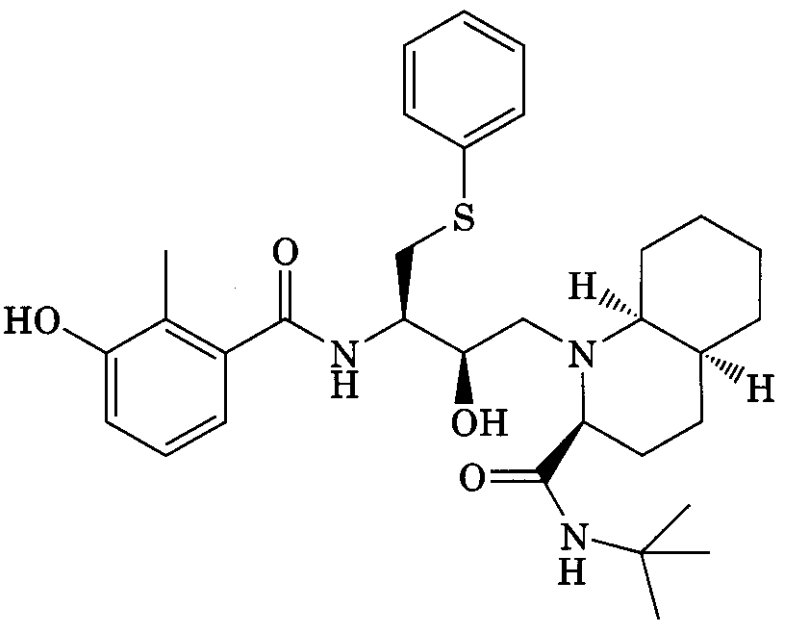
was already identified. Piracy of the decahydroisoquinoline tert-butylamide from (31) provided the idea for the hybrid molecule (40). In addition to the charged group, use of this ring system would partly "preorder" the inhibitor's structure, lessening the entropic cost of binding. Molecular modeling was used with known structures of HIV-P–inhibitor complexes to evaluate this idea, and it was judged to be reasonable enough to justify the synthesis of (40) (104). This compound was subsequently shown to have much better pharmacokinetic behavior than its antecedents, consistent with improved solubility and dissolution.

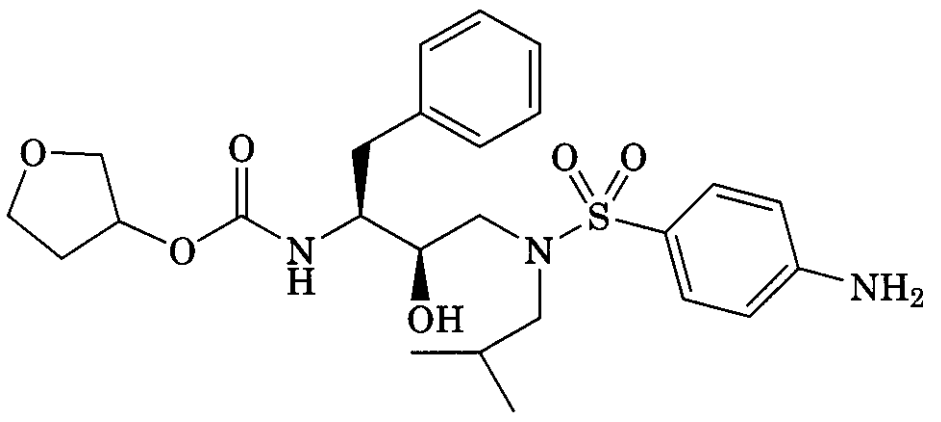
A convergent synthetic route was devised to generate (40) to improve the accessibility of important analogs. Although (40) was an 8 n*M* inhibitor of the isolated enzyme, better potency was needed for acceptable cell-based activity, and still better solubility characteristics were needed. A method for structure-based computational estimation of the interaction energy for HIV protease inhibitors with the enzyme was developed and used to help estimate inhibitor potency before synthesis (107). Variation of the group contributing the tertiary amine led to the discovery of the piperazine derivative (41) (L-732,747), which had subnanomolar potency against HIV-P. The X-ray structure of the HIV-P complex with (41) confirmed the binding mode predicted by molecular modeling, with the molecule filling the S_1, S_1, S_1', and S_2' pockets, and the S_3 pocket occupied by the terminal benzyloxycarbonyl moiety. Replacement of the benzyloxycarbonyl with more polar heterocycles, chosen to be accommodated by the S_3 pocket and to further improve aqueous solubility, yielded (37).

Several other approved AIDS drugs that act by inhibition of HIV-P have also been developed through use of SBDD methods. Compound (42) (amprenavir, Agenerase, also known as VX-478) is the most recent addition to the HIV-P inhibitors approved for human antiviral treatment, and differs significantly from earlier inhibitors. Compound (42) was specifically designed by Vertex scientists to minimize molecular weight to increase oral



(43) nelfinavir

bioavailability (108). Compound (43) (nelfinavir, AG-1343, also known as LY312857), like the precursors to the earlier drug (37) (indinavir), copied the decahydroisoquinoline *tert*-butylamide group from the first marketed HIV-P inhibitor (31) (saquinavir). Compound (43) was developed in a collaboration between scientists at Lilly and Agouron (109), and is mar-



(42) amprenavir