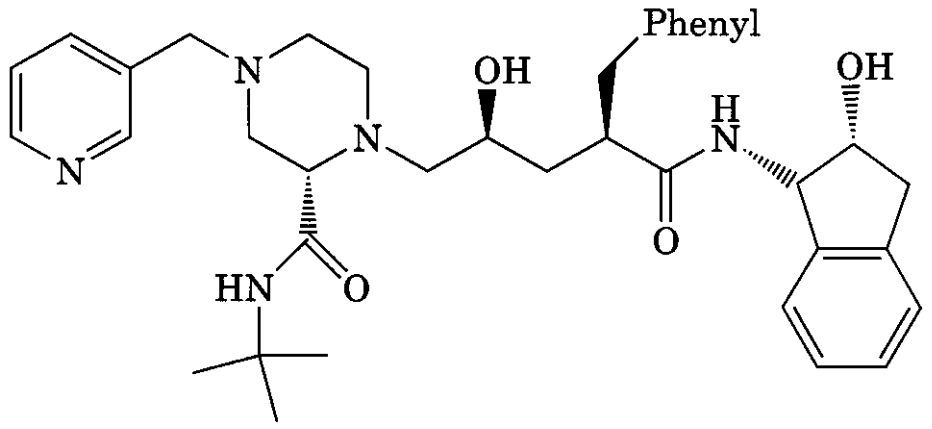


(37) indinavir

low solubility, which translates to low bioavailability. The discovery of (37) (indinavir, L-735,524) was the result of the successful application of SBDD at Merck to directly address this problem. During an iterative optimization process, the physicochemical properties of HIV-P inhibitors were modified within constraints that were established structurally (104). Crixivan (the sulfate of 37) was successfully launched for use as an antiviral drug.

The process leading to indinavir (Fig. 10.13) began with (**38**), a hydroxyethylene-containing heptapeptide mimic, originally designed as a renin inhibitor (105). The inhibition of HIV-P by (38) was discovered by screening. Classical medicinal chemistry methods allowed a reduction in size, and the discovery of an amino-2-hydroxyindan moiety to replace the terminal dipeptide (corresponding to $P_2'$, thought to bind into the $S_2'$ site). This approach (105, 106) resulted in the generation of (39)(L-685,434). Although (39) had a subnanomolar $IC_{50}$ for inhibition of HIV-P, it also had very low aqueous solubility, like most peptidomimetics. One way to improve solubility is to insert a charged functional group into the molecule. The tertiary amino group in the HIV-P inhibitor saquinavir (31)

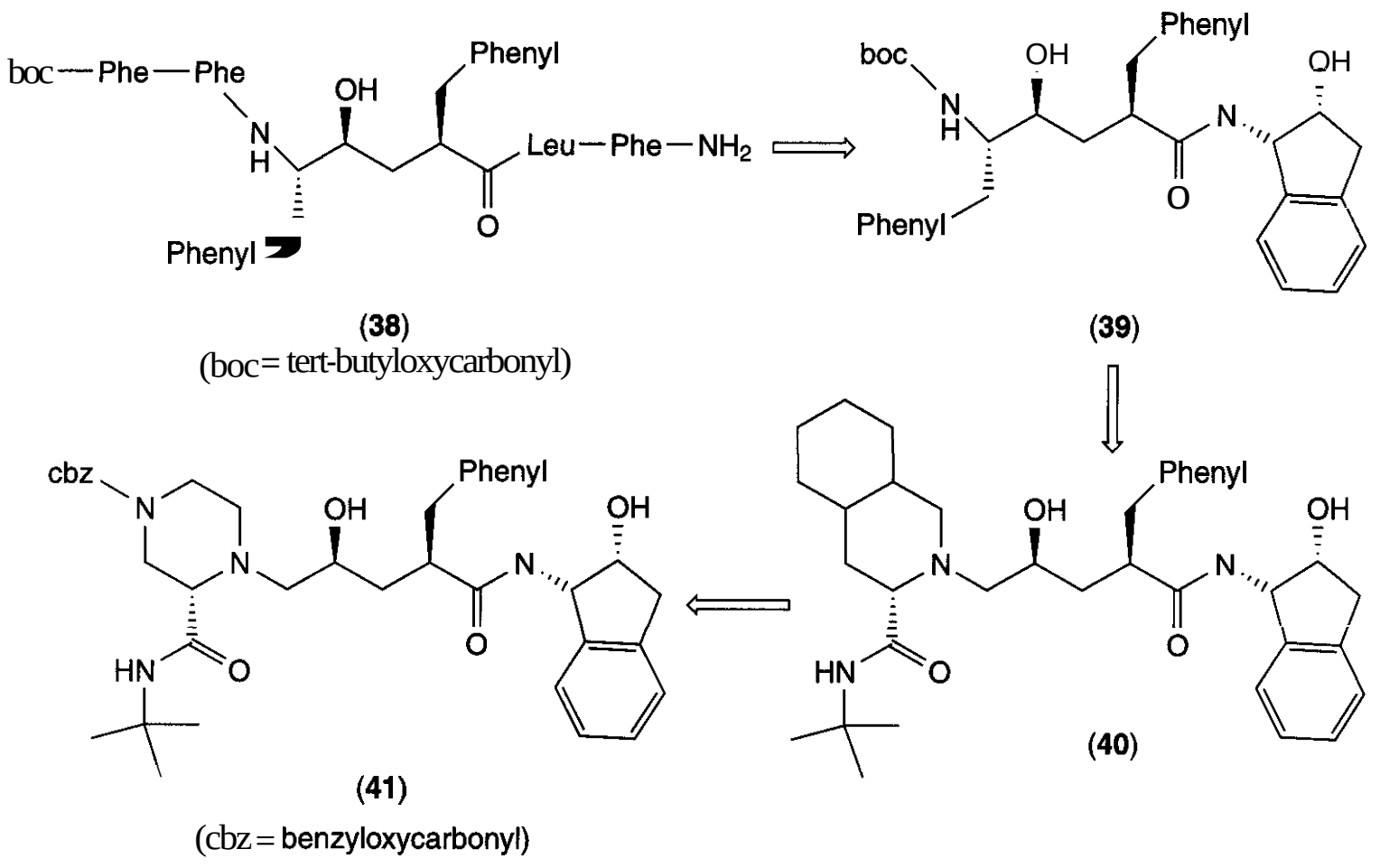


Figure 10.13. Structures of HIV-P protease inhibitors during the optimization process leading to the discovery of (**37**) (indinavir).