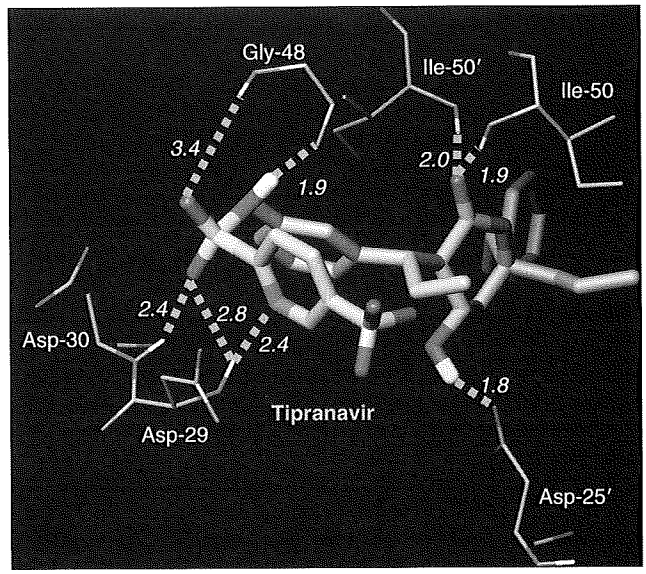

FIGURE 6 Hydrogen bond interactions of TPV with protease. Hydrogen bond interactions of TPV with Asp-29 and Asp-30 in the S2 subsite, with a catalytic aspartate (Asp-25′), and with flap residues Gly-48, Ile-50, and Ile-50′. The hydrogen bonds are shown in green dashed lines. The figure was generated using Maestro version 7.5.

no antiretroviral drugs or agents are likely to be completely specific for HIV-1 or to be devoid of toxicity or side effects, which has been a critical issue because patients with AIDS and its related diseases will have to receive antiretroviral therapy for a long period of time, perhaps for the rest of their lives. Thus, the identification of new class of antiretroviral drugs which have a unique mechanism(s) of action and produce no or minimal side effects remains an important therapeutic objective.

A variety of novel anti-HIV-1 agents that target different steps in the HIV replication cycle are currently in preclinical trials and will undoubtedly improve our ability to manage HIV-1 infection when they are duly introduced into clinics. However, as has been the case with RTIs and PIs, the development of drug resistance will likely limit the effectiveness of these drugs as well. Thus, a key element in future drug design strategies will be to understand how drug resistance mutations affect the interaction of the drug with its target, and to develop compounds with the adaptability to inhibit these variants along with wild-type HIV-1. New generation RTIs and PIs have already shown promise in accomplishing this task, by utilizing knowledge of the molecular, biochemical, structural, and thermodynamic nature of drug resistance. This should serve as a model in the design of more effective anti-HIV-1 therapeutics.

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