increase the trough concentration to enable once- or twice-daily dosing.[87] HIV-1-infected patients treated with BMS-663068 for 8 days with or without ritonavir boosting demonstrated a robust antiviral response with a drop in viral load of 1.21–1.73$\log_{10}$ copies mL^{-1}. BMS-663068 is currently in Phase 2 clinical trials for the treatment of HIV-1 infection.[87]

12.5 Prodrugs Designed to Exploit Carrier-mediated Mechanisms

It is becoming increasingly evident that membrane-associated transporter proteins such as peptide, nucleoside, ion, bile acid or vitamin transporters play an important role in shuttling drugs in and out of cells and consequently they play an important role in drug disposition and toxicity.[88,89] The ability to leverage transport proteins to assist in the delivery of poorly absorbed drugs across biological membranes, either to improve bioavailability or to enable tissue targeting, would be of significant value. Several antiviral prodrugs have taken advantage of removable promoieties that allow prodrug coupling to transport proteins with the objective of improving parent drug bioavailability (Figure 12.1C).

Acyclovir (ACV) (**32**, Figure 12.16) is a selective antiherpetic agent used in the treatment of herpes simplex virus (HSV-1, HSV-2) and varicella zoster virus (VZV) infections.[90,91] Although ACV proved to be very effective at inhibiting HSV in cell culture and was safe when administered systemically, it exhibited low oral bioavailability (15–20%), a short plasma half-life and limited aqueous solubility (~0.2%, 25 °C).[5,92] In an attempt to address these limitations, water-soluble esters of ACV were prepared, leading to the valine ester prodrug valaciclovir (**33**, Figure 16).[92] Valaciclovir demonstrated increased oral bioavailability, attributed to carrier-mediated intestinal absorption. It was

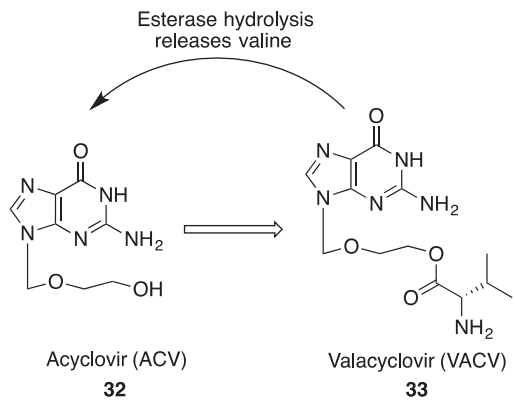

Figure 12.16 Valacyclovir (VACV) (**33**) is the valinate ester prodrug of the antiherpes agent acyclovir (ACV) (**32**). The valine prodrug allows coupling to the intestinal peptide transporter hPEPT1 to improve the oral bioavailability of acyclovir.