10, 30, and 100 mg kg^{-1} were selected for the efficacy study. In addition, we opted for bid dosing to ensure that plasma drug levels remained above the protein-adjusted EC_{90} throughout the 7 day study, thereby reducing the possibility of viral resistance that can occur with monotherapy treatment regimens.

The PXB mice were infected with HCV genotype 1a virus and after 5–8 weeks were treated with prodrug **32** at 10, 30, or 100 mg kg^{-1} bid. All doses of prodrug **32** produced a rapid and robust drop ($\sim$1log$_{10}$) in HCV viral mRNA titers (viral load) within 12 h of the first dose (Figure 5.15).[38] The maximum viral load reduction of $\sim$4log$_{10}$ units occurred by day 4 for all prodrug dose groups. The two higher doses of **32** (30 and 100 mg kg^{-1}) maintained viral suppression throughout the 7 day treatment period, at which point the average viral load reduction was -3.4 and -3.6log$_{10}$ units, respectively. By day 7, a dose-dependent decrease in viral load was apparent as the low dose of **32** (10 mg kg^{-1}) showed evidence of viral breakthrough (mean log reduction of –2.55). There was no evidence of drug accumulation in the plasma or liver over the 7 day treatment period for the dose groups. Two positive controls were included in the study, a non-nucleoside NS5B polymerase inhibitor (HCV-796) and an NS3/4A protease inhibitor (BILN-2061). Both HCV-796 and BILN-2061 have demonstrated efficacy in human HCV clinical trials and in HCV-infected chimeric mouse models similar to that described here.[61,62] In our study, both positive controls reduced the HCV viral load by $\sim$1.5–1.8log$_{10}$

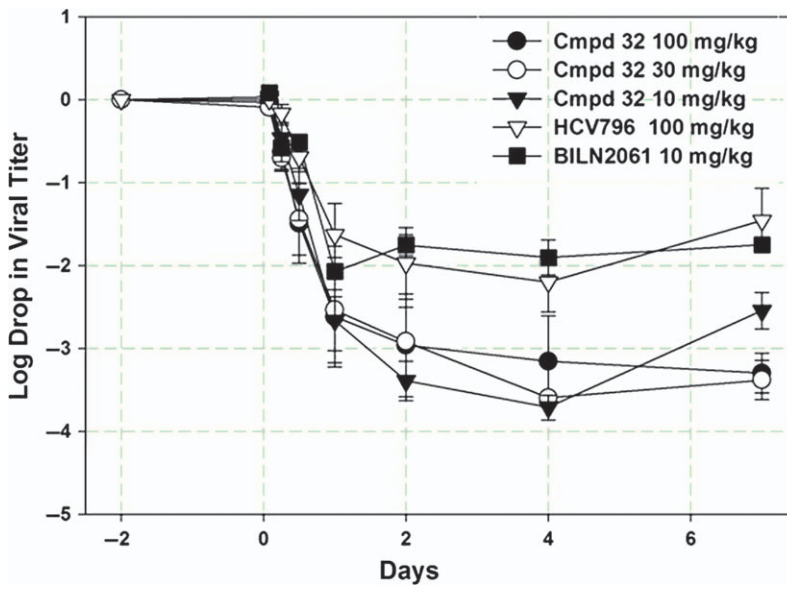

Figure 5.15 Reduction in HCV viral titers in plasma of PXB mice after infection with HCV genotype 1a and treatment with prodrug **32** or positive controls (HCV-796 or BILN-2061).