Table 5.5 Pharmacokinetic parameters of (+)-**57a** in four species.

	i.v. (1 mg kg^{-1})				*p.o. (5 mg kg^{-1})*	
Species	*Cl (mL min^{-1} kg^{-1})*	*Cl (% hepatic blood flow)*	*$T_{\frac{1}{2}}$ (h)*	*V_{dss} (L kg^{-1})*	*$AUC_{0-\alpha}$ (μg h mL^{-1})*	*F (%)*
Mouse	19	22	0.4	0.6	1.0	12
Rat	25	38	2.0	2.0	3.1	92
Dog	6.0	16	2.0	0.7	25	>100
Monkey	3.0	14	4.0	0.7	25	97

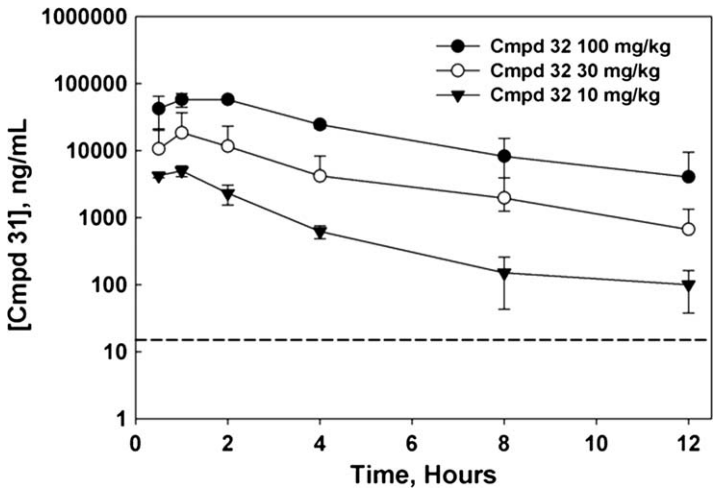

Figure 5.14 Drug plasma concentrations of **31** achieved upon p.o. administration of prodrug **32** to PXB mice prior to infection with HCV. The dashed line represents the serum-shifted EC_{90} (14 ng mL^{-1}) for **31** *versus* the HCV genotype 1a virus used to infect the PXB mice.

chimeric 'humanized' mice. The PXB mice are uPA/SCID mice with livers that have been repopulated with 70–90% human hepatocytes.[60] As a result, the mice can be infected with human liver pathogens such as HCV and HBV. We decided to use the PXB model to test whether an HCV antiviral agent that interacts with NS4B can inhibit viral replication *in vivo*.

Prodrug **32** was selected for use in the efficacy study, in part due to the high plasma drug exposures obtained in the rat PK studies. To ensure that the prodrug would also perform well in the efficacy model, the pharmacokinetic profile of **32** was determined in PXB mice prior to infection with HCV (Figure 5.14).[37] Oral administration of **32** at doses of 10, 30 and 100 mg kg^{-1} resulted in a linear increase in plasma drug exposure of **32** ($AUC_{0-12\,h}$ = 15, 66, 280 μg h mL^{-1}, respectively). In both dose groups, the 12 h plasma concentrations ($C_{12\,h}$) of **31** were well above the serum-shifted EC_{90} (14 ng mL^{-1} as determined using a genotype 1a replicon assay). Based on the PK data, doses of