Table 7.29 Pharmacokinetic parameters for the potassium salt of **14** (MK-5172)[a]

Species	*Cl (mL min^{-1} kg^{-1})*	*V_d (L kg^{-1})*	*$t_{\frac{1}{2}}$ (h)*	*p.o. AUC (μM h)*	*p.o. [liver] 4 h (μM)*	*p.o. [liver] 24 h (μM)*
Rat	28	3.1	1.4	0.7	23	0.2
Dog	5	0.7	3.0	0.4	nd	1.4

[a]Rat i.v. (2 mg kg^{-1}, $n = 3$, DMSO), dog i.v. (0.5 mg kg^{-1}, $n = 3$, DMSO), rat p.o. (5 mg kg^{-1}, $n = 3$, PEG400), dog p.o. (1 mg kg^{-1}, $n = 3$, PEG400).

(23 μM at 4 h), and at 24 h the liver concentration of MK-5172 was 0.2 μM, which is >25-fold higher than the IC_{50} in the replicon assay with 50% NHS.

When dosed intravenously to dogs, MK-5172 shows a low clearance of 5 mL min^{-1} kg^{-1} and a half-life of 3 h; it also has good plasma exposure (AUC = 0.4 μM h) after a 1 mg kg^{-1} oral dose (Table 7.29). Dog liver biopsy studies showed that the liver concentration of MK-5172 after the 1 mg kg^{-1} oral dose is 1.4 μM at the 24 h time point. Similarly to its behavior in rats, MK-5172 demonstrates effective partitioning into liver tissue and maintains a high liver concentration, relative to potency, 24 h after oral dosing in dogs.

In summary, initial screening for gt3a activity along with molecular modeling led to the discovery of a series of P2 quinoline macrocycles with excellent broad activity against NS3/4a genotypes and clinically observed gt1b mutant enzymes. This series was optimized for enzyme activity and liver exposure in preclinical species and led to the second-generation NS3/4a protease inhibitor MK-5172. Further studies of MK-5172, including clinical investigations of the PK and efficacy profile, are ongoing.[45]

7.5 Conclusion

The path to the development of HCV NS3/4A protease inhibitors has been a long one, but has now successfully yielded two marketed drugs, Victrelis and Incivek/Incivo, with multiple other compounds entering into late-stage clinical development, including the three compounds simeprevir (TMC-435350), vaniprevir (MK-7009) and MK-5172 that are the focus of this discussion. Ongoing and future clinical studies with these compounds, particularly in combination treatment regimes, will provide additional data, but HCV protease inhibitors appear well-positioned to play an important role in the rapidly evolving standard of care for treatment of HCV infections.

From a medicinal chemistry perspective, the structural properties of the inhibitors described in detail here do not conform well to what has been considered druggable space.[122–125] With high molecular weights in the 750 g mol^{-1} range and large polar surface areas, identification of compounds that show good plasma pharmacokinetics represents a significant accomplishment. Although structural chemistry has provided some key guidance in the design of new inhibitor structures, a significant portion of the optimization,