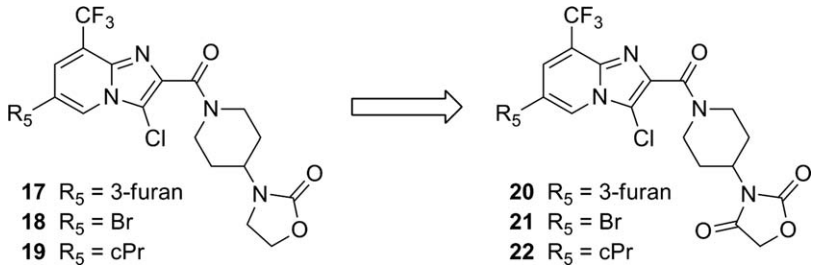

Figure 5.7 A series of oxazolidinones (**17**–**19**) were identified that potently inhibit HCV replication but undergo rapid metabolism *in vivo* to the corresponding oxazolidinediones (**20**–**22**). The diones were found to induce mRNA production of cytochrome P450s in rat and human hepatocytes.

displayed an acceptable PK profile in multiple species. Unfortunately, the low cLog*P* (2.6) associated with **17** did not translate to high aqueous solubility ($1.5\,\mu g\,mL^{-1}$ in fasted-state simulated intestinal fluid), which ultimately manifested in the inability to obtain high plasma drug exposures in the rat upon escalating the dose (Figure 5.8a). Surprisingly, the bromo-variant **18** was able to achieve much higher plasma drug levels in the rat relative to **17** (Figure 5.8a), albeit with a slight drop in replicon activity (EC_{50} of 31 nM *versus* genotype 1a replicon).

Compound **18** was advanced into a rat 7 day dose-range finding (DRF) study and was well tolerated up to $2000\,mg\,kg^{-1}$ per day. However, the toxicokinetic (TK) profile showed a dramatic drop ($\sim$80%) in plasma drug exposure from day 1 to day 7 (Figure 5.8b). We also observed high plasma concentrations of a circulating active metabolite (**21**, EC_{50} of 73 nM), which was formed upon oxidation of the oxazolidinone group. The time-dependent decrease in drug exposure and histological evidence of hepatocellular hypertrophy were indicative of drug-induced metabolism. In many such cases, induction of metabolism results from drug activation of nuclear receptors such as pregnane X receptor (PXR), constitutive androstane receptor (CAR), or aromatic hydrocarbon receptor (AhR) that result in upregulation of xenobiotic metabolizing enzymes. Both **18** and its metabolite **21** were profiled for enzyme induction in rat hepatocytes and **21** was shown to induce mRNA production of a number of cytochrome P450s at physiologically relevant concentrations. The two compounds also induced CYP mRNA levels in human hepatocytes, suggesting that drug-induced metabolism would also occur in humans. Although oxazolidinone substitution yielded potent HCV replicon inhibitors, the rapid *in vivo* metabolism to form the oxazolidinedione (*i.e.* **20**–**22**) caused considerable concern for potential drug–drug interactions. Efforts to block oxidation and formation of the oxazolidinedione metabolite were unsuccessful and the series was ultimately terminated. However, we were successful in replacing the C5 furan (**17**) or bromo (**18**) substituents, both of which significantly increased MW and lipophilicity. Ultimately, the C5-cyclopropyl exhibited the optimum balance of potency *versus* physicochemical properties as