re-establishment of the original scaffold pseudo-ring system. With this design, the benzyl is placed in the desired hydrophobic pharmacophore region, thereby maintaining a favorable region B alignment.

An initial carbamoylpyridone inhibitor **15** provided a high antiviral potency against a wild-type HIV-1 strain from a very simple scaffold. Even in the presence of human serum albumin (HSA), a potency reduction of only 12-fold resulted in 120 nM (38.4 ng mL^{-1}) as the protein adjusted IC_{50} in an MT4 cell-based antiviral assay ($^{MT4}PAIC_{50}$). This agent did not show sufficient efficacy against three clinically relevant RAL-resistant mutants (Table 6.1); nevertheless, it was comparable or slightly improved when compared with RAL or EVG. Furthermore, animal PK studies provided good $t_{\frac{1}{2}}$ (3.79–5.31 h), consistently low i.v. clearance ($Clt = 0.84$–2.44 mL min^{-1} kg^{-1}) and moderate bioavailability ($F = 22.2$–53.4%) across species, with the rat data shown in Table 6.2. Most importantly, good coverage of plasma concentration over the $^{MT4}PAIC_{50}$ of 38.4 ng mL^{-1} was observed in every species at 24 h post-dosing (5 mg kg^{-1} oral dose). Moderate molecular weight and good solubility combined with neither significant CYP inhibition nor metabolic concern suggested that this was an excellent starting point for further optimization.

A first attempt at further modification was the replacement of the C2 ester unit with an amide unit. It was unsuccessful because of an unfavorable intramolecular hydrogen bonding or steric hindrance that breaks the planarity of the chelating core unit, which is required for effective binding to the two active site metals (data not shown). Cyclization of the amide unit was a logical means to address both removal of the ester and alleviation of the amide planarity issue in order to reconstruct the metal chelation motif coplanarity. Hence this bicyclic carbamoylpyridone core unit was derivatized towards cyclized subclasses, represented by **16**–**18** shown in Tables 6.1 and 6.2. The inhibitors are differentiated by a linkage, by the presence of unsaturation in the new ring or by the addition of a hydroxyl group, in the case of **18**. As was expected, every derivative exhibited high antiviral potency against the wild-type strain and acceptable potency shift in the presence of HSA. Although inhibitors **16** and **17** do not have sufficient efficacy against Q148K, one of resistant mutants for RAL, inhibitor **18** showed improvement with only a 2.1-fold change. Conversely, the rat PK profiles for bicyclic analogs **16** and **17** were encouraging, but low oral bioavailability of the hydroxyl derivative **18** raised concerns and left room for improvement. In addition, the hemiaminal functionality is not only a chiral center but quickly racemized after chiral separation, presumably via equilibrium of the open-chain aldehyde form.

As had been done in progressing from the monocyclic amide to the bicyclic derivatives to address the issue around coplanarity and its effects on potency, we again resorted to the formation of a ring to solve a completely different challenge in the case of the hydroxyl analog **18**. Formation of the tricyclic ring system **19** again resulted in high potency against the wild-type virus and a low protein-adjusted IC_{50} and, similarly to the hydroxyl derivative, the tricyclic version had only a threefold change against the Q148K site-directed mutant that was being used as a surrogate measure of the ability to address clinically