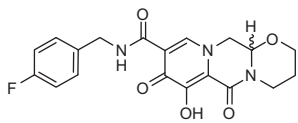
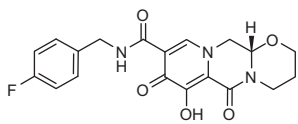
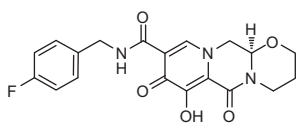
Table 6.2 Rat pharmacokinetics for carbamoylpyridone integrase inhibitors.

Compound	*Clt* ($ml\,min^{-1}\,kg^{-1}$)	$t_{1/2}$ (*h*)	V_{dss} ($L\,kg^{-1}$)	*F* (%)	$C_{24}\,h/^{MT4}PAIC_{50}$
15	1.16	4.67	0.19	53.4	3.4
16	0.02	10.5	0.01	39.5	2600
17	0.51	3.36	0.12	40.6	27
18	0.24	7.6	0.14	13.6	117

Table 6.3 Antiviral activity and pharmacokinetics for **19**.

Compound	*Structure*	$^{pHIV}IC_{50}$ (μM)	$^{pHIV}PAIC_{50}$ (μM)	*Q148K* (*FC*)	*Cl* (*ml* min^{-1} kg^{-1})	*F* (%)
19		0.002	0.019	2.8	0.10	51
19*S*		0.002	0.081	2.4	0.10	79
19*R*		0.002	0.009	11	0.17	52

relevant resistance mutations. Also encouraging was the fact that the tricyclic compound **19** had a very low i.v. clearance in rats, along with the best half-life observed thus far and over 50% oral bioavailability (Table 6.3).

6.3.3 Execution and Delivery of the Tricyclic Carbamoylpyridone

Once robust activity and scaffold properties had been established, our program moved to a single-round pseudotyped antiviral luciferase reporter assay (pHIV),[91] for improved throughput and biosafety concerns. Tricyclic carbamoylpyridone **19** was also a potent antiviral (IC_{50} 2 nM) in the pHIV assay while demonstrating a similar threefold loss in activity against the Q148K mutant virus, as was observed previously in the MT4 assay system. Additionally, a modest protein binding shift of tenfold resulted in a protein-adjusted IC_{50} ($^{pHIV}PAIC_{50}$) against the resistant virus of 53 nM.

This virological profile was a significant advance toward our goal. However, this data set was from the racemate and the concern over differential potency,