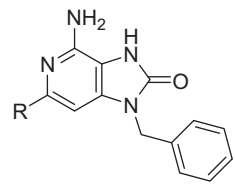
34 were active as TLR-7 agonists. The potency was generally similar to or slightly better than the oxopurine parent **31**. Although **34**, which has an additional methyl group, was more active, for synthetic ease **32** was further optimized.

The next phase of optimization addressed the issue of metabolic stability.[46] As shown in Figure 10.13, the parent core was reasonably stable based on intrinsic *in vitro* clearance by human liver microsomes (HLMs). Compound **41** is illustrative; however, this compound has an EC_{50} >4000 nM, indicating that a substituent at C2 is required for TLR-7 agonist activity. Methyl and small linear alkyl groups at C2 did not introduce metabolic liabilities relative to H, as illustrated by **32** and **42**. However branched alkyl substituents were susceptible to metabolism, such as the isopropyl in **43**. In this series, a trifluoromethyl group (**44**) gave the best combination of potency (EC_{50} = 102 nM) and metabolic stability, despite a somewhat high logD (3.3).

Compound **44** became PF-4171455 and was the subject of further investigation. In rat pharmacokinetic studies, **44** had a clearance of 33 μL min^{-1} kg^{-1} and an oral bioavailability as high as 71% when administered as a nanosuspension. When administered intravenously to dogs, the clearance was 6 μL min^{-1} kg^{-1}. A prediction of the human half-life based on allometric scaling was 3–7 h. Fitting to a pharmakokinetics–pharmacodynamics model[47] indicated that **44** would generate efficacious levels of IFN-α in HCV patients at daily doses less than 50 mg.

PF-4171455 (**44**) met complications during development due to formulation problems associated with poor solubility. A series of analogs was explored to improve this property.[48] The initial strategy was to lower the lipophilicity by adding polar groups in the N9 substituent. Towards this end, a number of heterocyclic replacements for the phenyl ring were evaluated (Figure 10.14). Of several isomeric methylpyridines reported, **46** had the best balance of potency (50 nM) and solubility (22 μg mL^{-1}). Isomers **45** and **47** were inferior in both of



	R	EC_{50} (nM)	HLM (mL/min/mg)
41	H	> 4000	< 7
32	CH_3	1540	< 7
42	*i*-Pr	304	< 7
43	*n*-Pr	480	14
44	CF_3	102	< 7

Figure 10.13 SARs of the C2 substituent of 8-oxodeazapurines. Compound **44** is PF-4171455.