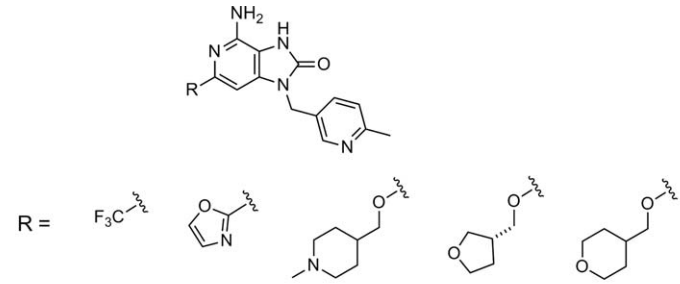

	46	51	52	53	54
EC_{50}(nM)	50	102	>4000	474	99
Sol (μg/mL)	22	66	--	--	17
rat cytosol $t_{1/2}$ (min)	46	46	--	--	>1000

Figure 10.15 SARs of the C2 position of 8-oxodeazapurines.

half-life was suggestive of aldehyde oxidase-mediated metabolism. The strategy to address these issues was to evaluate more polar groups at C2. Replacement of the lipophilic trifluoromethyl group by an oxazole (**51**) led to similar potency and a gain in solubility, but no improvement in aldehyde oxidase substrate liability. Introduction of charged polar groups, as in the tertiary amine of **52**, led to a loss of activity. Cyclic ethers such as **53** were found to retain good potency. The best member of this series was **54**, which contains a cyclic tetrahydropyran. This compound was comparable to the trifluoromethyl starting point **46** regarding potency and solubility, but was significantly more stable in rat cytosol. The half life of >1000 min indicated that **54** was not an appreciable substrate for aldehyde oxidase. Another favorable property of **54** was that it had less risk of polypharmacology as represented by the absence of inhibition activity toward adenosine receptors A1 and A2. Other analogs in this series had measurable, albeit low-level, activity towards these two receptors.

The rat pharmacokinetics of **54** were favorable and comparable to those of **44**. The fraction absorbed (40%) and bioavailability (17%) were somewhat lower and the half-life (0.4 h) was comparable. Based on these parameters and the improved potency, **54** was estimated to have an efficacious clinical dose for induction of IFN-α in HCV patients of <30 mg once per day. Compound **54** therefore satisfied the criteria of having substantially better solubility and thus better pharmaceutics properties than their earlier development compound **44** and accordingly was stated to be a back-up candidate. Additionally, issues of polypharmacology were successfully addressed.

10.5 Conclusion and Outlook

TLR-7 represents an attractive target for the identification of agonists that might possess utility to treat chronic viral hepatitis infection. Several programs