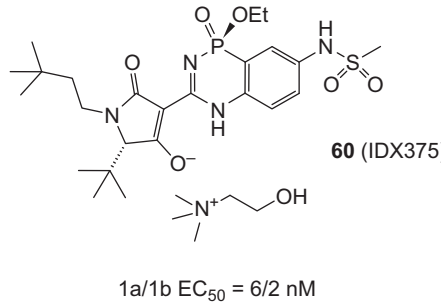

Figure 8.14 Structure of palm site 1 NS5B inhibitor IDX375 from Idenix Pharmaceuticals.

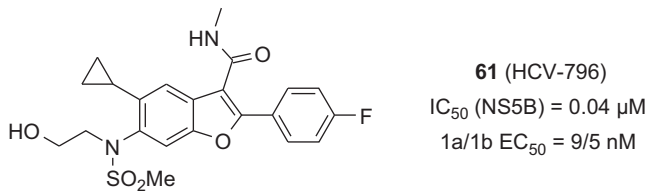

Figure 8.15 Benzofuran palm site 2 NS5B inhibitor HCV-796 from Wyeth/ViroPharma.

half-lives ($t_{\frac{1}{2}} = 30$–40 h) at doses of 200 mg administered once or twice daily. A 200 mg bid dose for 1 day resulted in a maximum 0.5–1.1$\log_{10}$ reduction in plasma HCV RNA.

8.3.4 Palm Site 2 Inhibitors

As part of a research collaboration that took place in the early 2000s between ViroPharma and Wyeth Research, a fourth series of allosteric NS5B inhibitors was discovered through screening of sample collections and produced clinical candidates. Early compounds (*e.g.*, HCV-086, $EC_{50} = 200$ nM) exhibited modest activity, poor metabolic stability and low solubility and had low efficacy in the clinic. Subsequent optimization to improve potency, ADME-PK and genotype profiles led to the discovery of HCV-796 (**61**, Figure 8.15) a benzofurancarboxamide derivative that displayed a very attractive preclinical profile and was the first NS5B allosteric inhibitor for which promising clinical activity was demonstrated in HCV-infected patients.

Unfortunately, neither the structure of the original screening hit nor the lead optimization process which led to the discovery of HCV-086 and HCV-796 has been reported in the literature. HCV-796 is a specific and reversible inhibitor of HCV NS5B polymerases from genotypes 1a/1b, 3 and 4 ($IC_{50} = 0.01$–0.57 μM) and has reduced potency against genotype 2 ($IC_{50} = 1.7$ μM). It is non-competitive with respect to substrates NTPs and RNA template and acts at the