ring system may be less critical than originally thought, opening the door to still new structurally diverse analogs.[78,80]

8.3.3.3 *Benzothiadiazines from Anadys Pharmaceuticals*

In 2008, Anadys Pharmaceuticals began to disclose their work on benzothiadiazine palm site 1 NS5B inhibitors, which ultimately led to the discovery of setrobuvir, currently in Phase 2 clinical trials. Based on a computational analysis of NS5B allosteric sites, which suggested that the palm domain was well conserved across gt1 HCV, efforts were focused on molecules that bind to this site and, more particularly, on the benzothiadiazine class for which potent starting points and structural information were available from the literature. Using a structure-guided approach and building on previously published knowledge, initial efforts led to a series of pyridazin-2-one des-A-ring analogs (*e.g.*, **57**, Figure 8.13) reminiscent of the pyridone analogs (*e.g.*, **56**) described by Abbott Laboratories.[79,81] While very potent inhibitors of the gt1b-HCV replicon were rapidly identified, most of the challenges lay in the optimization of the pharmaceutical and DMPK profiles of this class of molecules (*e.g.*, aqueous solubility, lipophilicity and bioavailability). Indeed, advancement of molecules such as **57** was compromised by their high polar surface area (PSA = 203 Å^2), resulting in low permeability, high efflux ratio and very low bioavailability in preclinical animal species.[81] Although some understanding of the parameters that negatively impacted the DMPK profile of these molecules led to some modest improvements (10–15% bioavailability), these could not be achieved without compromising the antiviral potency profile (EC_{50} = 110–320 nM) and focus was switched to an alternative strategy.

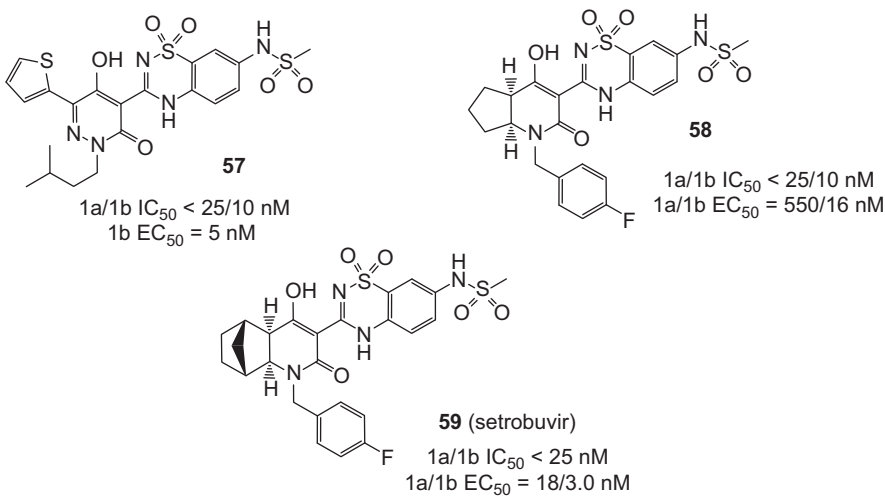

Figure 8.13 Palm site 1 inhibitors from Anadys Pharmaceuticals and discovery of setrobuvir.