Several structure-based modifications to the AB-ring system (*e.g.*, pyrrolo[1,2-*b*]pyridazin-2-ones) combined with modifications of the benzothiadiazine moiety (*e.g.*, dioxoisothiazoles, benzothiophene dioxides, benzothiazines) aimed at reducing the PSA and improving permeability were explored, again leading to the discovery of very potent molecules, but low bioavailability remained a persistent issue for these derivatives also.[78] The subsequent strategy investigated saturation of the A-ring system as a means to disrupt planarity in this part of the molecule, decrease PSA and improve bioavailability. Dihydropyridin-2-ones offered the first hints of success for this approach as the modification was well tolerated and excellent replicon potency was maintained for gt1b. Furthermore, analogs such as **58** (Figure 8.13) exhibited good metabolic stability, low clearance and some improvement in permeability ($P_{app} = 1.6 \times 10^{-6}$ cm s^{-1}), resulting in moderate bioavailability (24%) in cynomolgous monkeys.[82]

In order to address the lower potency seen in the gt1a replicon compared with 1b ($EC_{50} = 550$ and 16 nM, respectively), a novel AB-ring modification containing a saturated tricyclic dihydropyridinone motif was designed, which led to the selection of the clinical candidate setrobuvir (**59**). The rationale behind the design of this structural motif was derived from examining X-ray crystal structures of analogs such as **58** bound to palm site 1 of NS5B.[83] Analysis of the shallow surface pocket interacting with the cyclopentane moiety of **58** suggested that more space-filling groups could be accommodated in this area and possibly lead to potency improvements. Modeling of compounds such as **59** into palm site 1 suggested that the orientation and all key interactions would be maintained between the ligand and the protein. Moreover, the bicyclic moiety of **59** appeared to fulfill the objective for which it was designed, *i.e.*, increasing occupancy of the sub-pocket. Several saturated, unsaturated and heterocyclic versions of fused pyridinones were evaluated in addition to different bridge sizes. In the end, compound **59** (setrobuvir) emerged as an analog with excellent antiviral potency against gt1a/1b-HCV ($EC_{50} = 18/3$ nM), good solubility (>100 μg mL^{-1}) and good plasma exposure levels in cynomolgous monkeys, consistent with its *in vitro* metabolic profile and low *in vivo* clearance. Oral bioavailability (52% in monkeys) was also improved over previous analogs, even though apparent permeability in Caco-2 cells remained low for this compound (1.3×10^{-6} cm s^{-1}). Unfortunately, further information on the compound's profile must await future publication. Setrobuvir (formally ANA598) is currently in Phase 2 clinical trials and is being developed by Roche following their acquisition of Anadys in October 2011 (see below).

8.3.3.4 Benzothiadiazines in Clinical Development

Four palm site 1 NS5B inhibitors are currently in clinical development. Two benzothiadiazine derivatives, ABT-072 and ABT-333 (the structures of these compounds have not yet been disclosed), were simultaneously progressed into the clinic by Abbott Laboratories. Both compounds are potent inhibitors of gt1a/1b HCV with EC_{50} <10 nM and are considerably less potent against