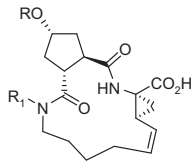
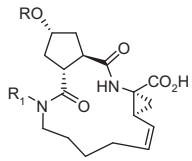
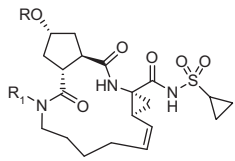
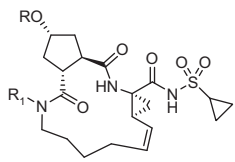
Table 7.2 (*Continued*)

Compound	*Structure*	R_1	*Ring size*	*HCV NS3 1a K_i (nM)*	*HCV NS3 1b EC_{50} (nM)*
44		H	14	260	>10000
45		Me	14	44	2200
46		H	14	2.2	4400
47		Me	14	0.41	9.1

In contrast, a free hydrazine (**42**) maintains biochemical potency while also showing some activity in the replicon assay (7.6 μM). Although the cyclopentene-based inhibitor **43** is similarly potent, the difficulty of synthesis and potential of irreversible covalent attachment *via* the core Michael acceptor led to the decision to focus on the cyclopentane analogs.

As has been demonstrated previously by Tibotec/Medivir[63] on proline-based macrocycles, the typically large P3 groups can be truncated significantly, including complete elimination of the R_1 substituent. Within this series of inhibitors, when $R_1 = H$ (**44**, Table 7.2) biochemical potency was maintained, but replicon activity was again lost. Simply capping the free NH with a methyl group (**45**) led to a more than fivefold improvement in replicon potency. Incorporation of the potency-enhancing carboxylic acid bioisostere cyclopropaneacylsulfonamide[64–66] then led to low- to sub-nanomolar inhibitors (**46**, **47**) which also possessed single-digit nanomolar replicon EC_{50} when the P3-capping group was methyl (**47**).

Building on **47**, additional SARs were developed in order to improve the moderate permeability ($P_{app} = 3.8 \times 10^{-6}$ cm s^{-1}), intrinsic clearance