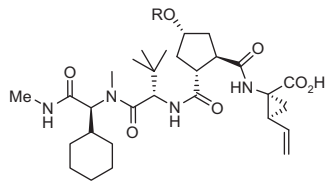
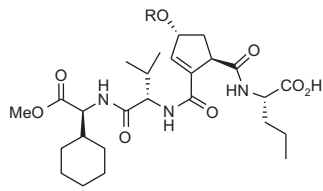
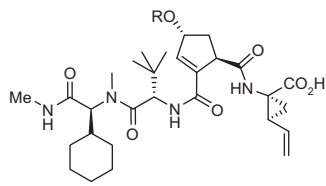
Table 7.1 (*Continued*)

Compound	*Structure*	*NS3 1a K_i (μM)*[a]
35		>10
36		0.1
37		0.0013

[a]Inhibition constants of full-length NS3/4a protease.

Following the successful implementation of the cyclopentane proline replacement, the corresponding cyclopentene-containing compounds were also prepared by a similar scheme.[61] Compared with the cyclopentane analogs, the cyclopentene analogs are generally more potent (Table 7.1). For example, even simple norvaline P1 analog **36** is a 100 nM inhibitor against gt1a, whereas the corresponding cyclopentane analog **29** is 2.3 μM. As was observed with the cyclopentane core analogs, introduction of vinylcyclopropane-containing P1 groups led to a large increase in potency, with **37** being a 1.3 nM inhibitor of gt1a.

With these promising results in hand, a further evolution was incorporation of the P1–P3 macrocyclization strategy utilized in BILN-2061 into the cyclopentane/cyclopentene core inhibitor series.[62] Given the differences inherent in the switch from proline to cyclopentane that have been discussed, an examination of various ring sizes was undertaken (**38–41,** Table 7.2) and clearly showed that the optimum ring size is 14, which is smaller than is present in BILN-2061, again demonstrating the difference between proline- and cyclopentane-based cores and also the interplay of P3/P4 *N*-substituents and P1–P3 macrocycle. The identity of the nitrogen R_1 substituent is also key to HCV NS3 activity. While a hydrazine carbamate R_1 group (**39**) leads to potent biochemical activity, activity in the cellular replicon activity is lost (>10 μM).[62]