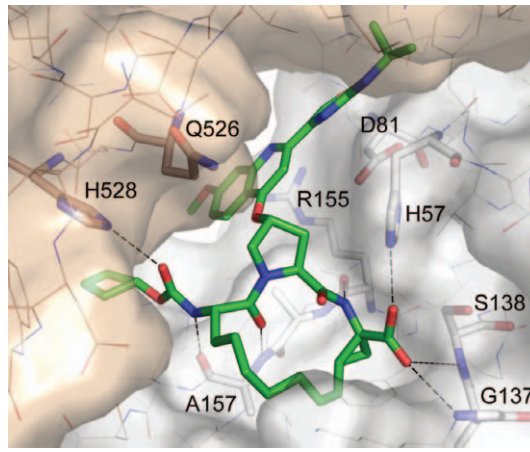

Figure 7.9 Model of **4** (green) bound to full-length NS3/4A (protease, white; helicase, light brown) with key protein–-inhibitor interactions shown.

to rationalize this, Merck chose to model **4** bound to the full-length NS3/4A protein, including the significantly larger helicase domain (Figure 7.9), to determine the extent of any role the helicase could play in inhibitor binding. The specific role of the helicase in binding has been the subject of debate in the literature,[82] although recent X-ray structures have confirmed that the helicase does make contact with NS3 inhibitors.[83] At the time, no full-length structures with inhibitors bound were available; consequently, a published *apo*-enzyme structure[84] was used as the starting point for docking studies. To permit access of the inhibitor to the active site, the six C-terminal residues (DLEVVT) of the helicase domain that lie in the active site of the *apo* X-ray structure were truncated.

Analysis of **4** docked in the latter structure suggested that the helicase domain could provide a surface over the P2 moiety, including a hydrophobic pocket that appeared to accommodate the thiazolyl substituent.

Specific inhibitor–helicase interactions in this model include His528–carbamate oxygen and Gln526–quinoline. The other key finding from this study was that there is space between the carbamate cyclopentane and the quinoline ring that could potentially accommodate a macrocyclic connection. This concept was supported by re-examination of the helicase C-terminus from the *apo* structure, overlaid with BILN-2061 (Figure 7.10) in which the side chain of Glu628 occupies the same space as the proposed linker. Together, these observations suggested that an alternative P2 quinoline–P4 cyclopentyl macrocyclization to form a structurally distinct series of inhibitors was feasible.

In order to test this hypothesis in a readily accessible system, the initial targets were carbamate derivatives **61**–**64** (**63** docked in Figure 7.11), in which the P1–P3 macrocyclic linker was disconnected, the proposed P2–P4 linker was formed and a simplified 3-phenylquinoline P2 was utilized. Energy scores for the different linker lengths calculated by two methods predicted that the five- and six-carbon linkers would show greatest activity (Table 7.9).