View Online

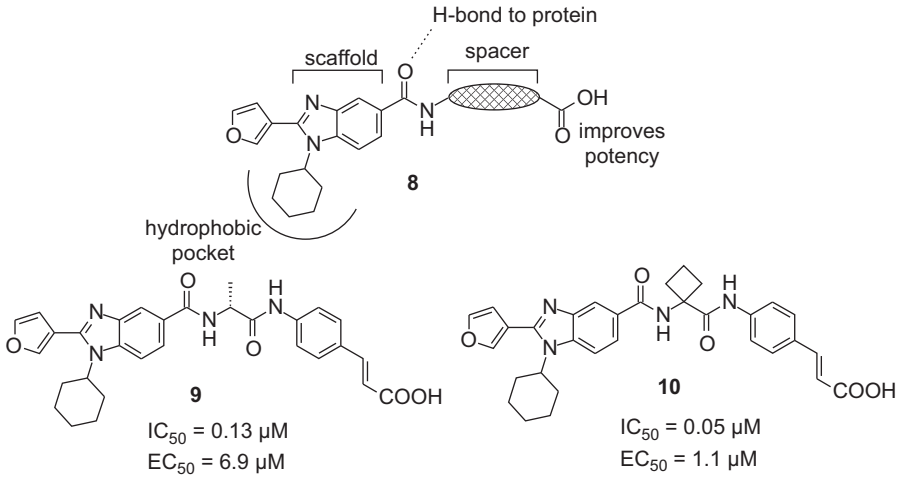

Figure 8.3 Discovery of benzimidazole inhibitors with novel diamide right-hand sides.

intrinsic and replicon potency, which upon further optimization led to achiral derivatives such as **10** with excellent intrinsic activity ($IC_{50} = 50$ nM), comparable antiviral potency to inhibitor **7** and improved physicochemical properties.[21] Diamide derivatives similar to **10** were used to select and characterize resistant variants using the replicon system. Gratifyingly, resistant mutations that emerged with this class of benzimidazole diamides were found to localize in the NS5B thumb domain and encoded amino acid substitutions at positions P495, P496 and V499, proximal to the region previously described in cross-linking experiments. Inhibitors were most sensitive to P495 mutants, which conferred the highest shifts in single-mutant replicon sensitivity (>80-fold shift).[16]

A key finding for the program occurred when efforts to improve permeability and cell culture potency led to the replacement of the benzimidazole scaffold with a more lipophilic indole isostere. Unexpectedly, this modification improved both intrinsic ands cell-based potency by two orders of magnitude, as shown in Figure 8.4 for the *N*-methylindole-6-carboxylic acid **11**, suggesting a more optimal interaction of the lipophilic indole nucleus compared with the more polar benzimidazole version. At this time, benzimidazole-based NS5B inhibitors had aroused interest from other companies and the IRBM-Merck group began reporting on similar observations.[22]

In addition to providing leads with greatly improved potency, the availability of an easily accessible position on the scaffold to explore new interactions with the protein quickly led to the simultaneous discovery by the Boehringer Ingelheim and IRBM-Merck groups of indole-*N*-acetamide derivatives such as **12** and **13**. An unexpected benefit from this class of inhibitors came about when both groups succeeded in generating X-ray data on NS5B–indoleacetamide complexes, revealing for the first time the exact location of the

Published on 17 June 2013 on http://pubs.rsc.org | doi:10.1039/9781849737814-00248
on 01/09/2013 10:32:14.