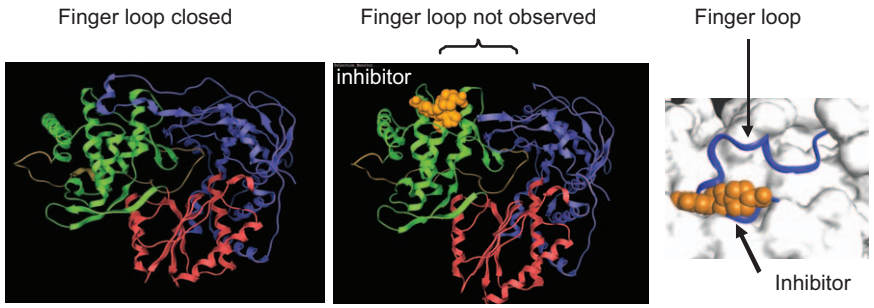

Figure 8.5 Apo NS5B enzyme (left) is depicted in ribbon form with the palm, thumb and finger domains shown in red, green and blue, respectively. The *apo* form shows an enclosed active site tunnel with the Λ finger loops protruding from the finger domain and interacting with the thumb domain. Upon binding of an inhibitor from the indoleacetamide class (center), the inhibitor (yellow) displaces the Λ finger loop and occupies the liberated binding pocket (thumb pocket 1). Finger loops are no longer visible in the structures as a result of increased mobility. An overlap between the inhibitor and a portion of the Λ finger loop (right) shows how they compete for the same binding space on the thumb domain. Copyright 2006, Thomson Reuters.[101]

of R503. The structural data were consistent with previously described cross-linking data and resistant-replicon selection experiments. Furthermore, hypotheses were beginning to emerge on a plausible mechanism of action for this class of allosteric NS5B inhibitors. The overlap between the inhibitor and the Λ1 loop binding sites suggested that inhibitors prevent closure of the finger loop on to the thumb domain and the formation of an enclosed active site tunnel, which may be necessary for RNA synthesis. Compounds from this class are now commonly referred to as 'finger loop inhibitors' and the allosteric binding site as 'thumb pocket 1.'

Optimization of indole-*N*-acetamide derivatives proceeded with matrices of compounds exploring various indole C2 substituents and acetamide combinations, eventually leading to very potent zwitterionic derivatives.[24] Following optimization of plasma protein binding/serum shift, off-target activity (*e.g.*, PXR activation associated with the nature of the acetamide side chain) and *in vivo* PK parameters, the IRBM-Merck group identified analog **14** (Figure 8.4), which, despite low bioavailability in rats, displayed improved properties in monkeys and dogs and was predicted to be a low-clearance drug in humans. This class of compound had only weak potential to form reactive acylglucuronide metabolites that could lead to toxicity and idiosyncratic reactions. The potential of **14** for further development was highlighted, but there have not been reports of this compound progressing into clinical development.[25]

At Boehringer Ingelheim, most of the focus remained on diamide derivatives (Figure 8.3). The excellent intrinsic potency of **10** was rationalized by NMR studies which established the ability of α,α-disubstituted amino acid linkers to