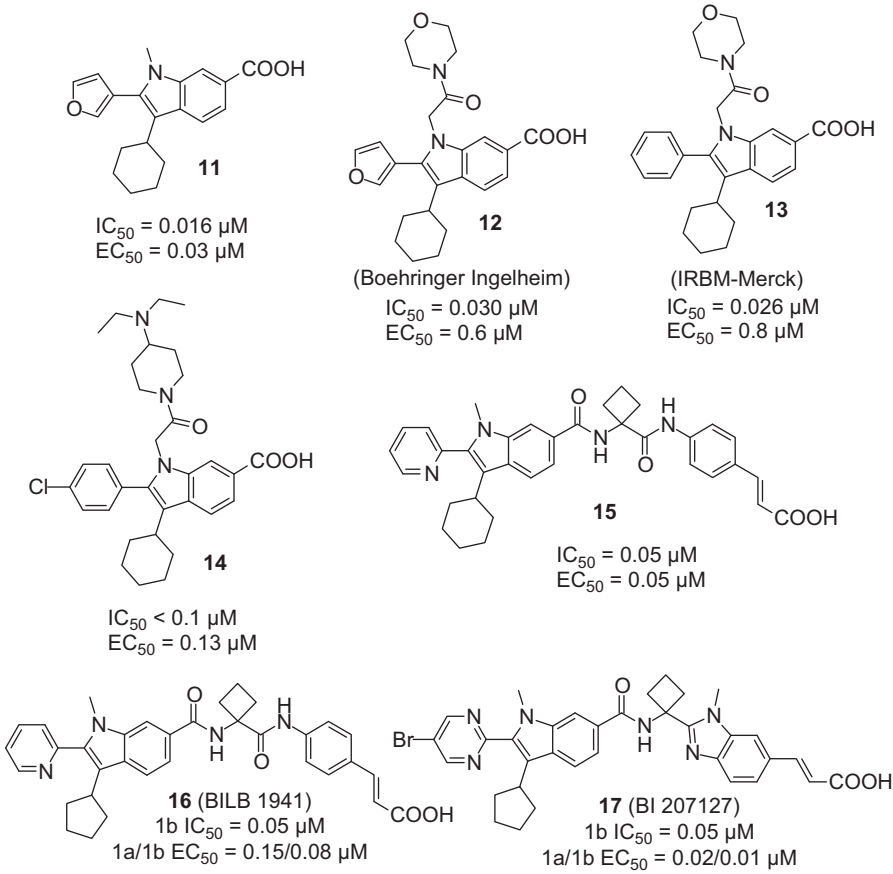

Figure 8.4 From benzimidazole to indole-based thumb pocket inhibitors.

benzimidazole/indole allosteric binding site and shedding light on a plausible mechanism of inhibition.[23] All previous efforts to co-crystallize or soak NS5B constructs with benzimidazole inhibitors had met with frustrating failure due to crystal cracking and poor diffraction data. These observations suggested possible protein conformational changes upon inhibitor binding, consistent with an allosteric inhibition mechanism. The structure of an indole-*N*-acetamide inhibitor bound to NS5B polymerase is shown in Figure 8.5.

Most striking is the loss of electron density for the Λ1 finger loop upon inhibitor binding, the displacement of which reveals a well-defined binding site, previously occupied by lipophilic side chains of loop residues. The cyclohexyl ring of the inhibitor occupies most of that lipophilic pocket, while the scaffold is stacked against the well-conserved proline residues (P495 and P496), providing a rationale for the preference of the indole scaffold over the more polar benzimidazole system. In addition, the carboxylic acid of indole-based inhibitors interacts through a salt bridge with the basic guanidinium side chain