synthesis.[11b] Like HIV-RT, HCV NS5B can be inhibited by nucleoside and nucleotide analogs (particularly those carrying 2′-ribose substitution) that are anabolized to their triphosphate derivatives and are incorporated by the enzyme to act as non-obligate chain terminators.[9] In addition, however, as drug companies began probing their corporate compound collections for potential NS5B inhibitors, a surprising array of structurally diverse chemotypes began to emerge that were shown through reversed genetics and resistance signatures or X-ray crystallography to bind to one of four distinct allosteric sites.[9] These non-nucleoside inhibitors (NNI), which bind in allosteric sites referred to as thumb pockets 1 and 2 and palm sites 1 and 2 depending on their location (Figure 8.1), interfere with protein conformational movements, which are thought to be necessary for RNA synthesis.

NNIs from all four allosteric sites have progressed into the clinic and demonstrated antiviral potency in HCV-infected patients, thus validating the mechanism by which they interfere with NS5B-mediated RNA synthesis. To date, more than 430 patent applications have been filed on structurally diverse molecules that claim to inhibit NS5B polymerase, qualifying this protein as the most 'druggable' HCV target. Recently, the topics of both nucleoside and non-nucleoside HCV NS5B inhibitors was comprehensively reviewed.[9]

This chapter does not attempt to provide exhaustive coverage of all published classes of NS5B inhibitors; rather, it focuses on successful drug design strategies that have led to the identification and the development of drug candidates from all four classes of allosteric NNIs (nucleoside and nucleotide inhibitors are discussed in chapter 12). The discussion will be structured according to inhibitor binding site.

8.3 Non-nucleoside NS5B Polymerase Inhibitors

8.3.1 Thumb Pocket 1 Inhibitors

8.3.1.1 Discovery of BILB 1941 and BI 207127

Approximately 12 years ago, Japan Tobacco and Boehringer Ingelheim (Canada) published consecutive patent applications disclosing closely related benzimidazole-5-carboxamide derivatives as specific inhibitors of HCV NS5B polymerase.[12] The initial hits (**1** and **2**, Figure 8.2) displayed similar potencies and were discovered through screening of proprietary corporate sample collections.[13]

Interestingly, optimization of these hits followed divergent paths. The observation that carboxylic acid derivatives were slightly more potent than amide derivatives (*e.g.*, **3**), led Japan Tobacco to focus their structure–activity relationship (SAR) work on optimization of the left-hand side C2 substitution of the benzimidazole-5-carboxylic acids.[13a] On the other hand, NMR-based techniques, such as differential line broadening (DLB), were used at Boehringer Ingelheim to identify portions of the initial hit that appeared to be interacting with the target protein. The data suggested that only portions of the hit's