

efficacy with improved safety and tolerability, while minimizing emergence of resistant virus.¹⁰ NS5B polymerase inhibitors are therefore expected to play a key role in the future treatment of chronic HCV infection.

8.2 The NS5B RNA-dependent RNA Polymerase

NS5B's primary function is to synthesize a virion's complementary negative RNA strand, which it then uses as a template to produce (+)-RNA for further translation into viral proteins necessary for replication and virion morphogenesis.⁸ As previously mentioned, NS5B exhibits low fidelity and is responsible for the broad heterogeneity observed in circulating virus and, hence, occurrence of drug-resistant viral strains. The 65 kDa protein shares the common folds of other nucleic acid polymerases with characteristic thumb, finger and palm domains, with two-finger loop residues enclosing the active site through interactions with the thumb domain (Figure 8.1).¹¹ Recently, the crystal structure of an NS5B construct bound to an RNA primer–template has shed some insight into structural requirements for substrate recognition and RNA

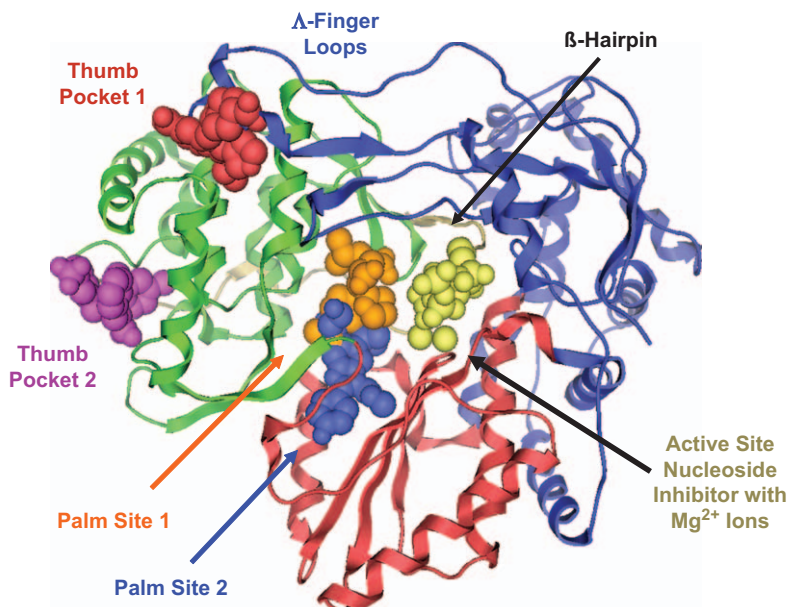


Figure 8.1 Three-dimensional structure of NS5B with allosteric inhibitor binding sites. The three-dimensional structure of NS5B is shown in ribbon representation with the palm domain colored red, the thumb domain green and the finger domain with the Δ finger loops blue. Inhibitor binding sites are depicted using CPK models of representative inhibitors: thumb pocket 1 (indoleacetamidocarboxylic acid; red), thumb pocket 2 (phenylalanine derivative; magenta), palm site 1 (acylpyrrolidine; orange), palm site 2 (benzofuran derivative; blue), active site (nucleoside analog with two Mg^{2+} ions; yellow). Copyright 2009, Informa Healthcare.^{9a}