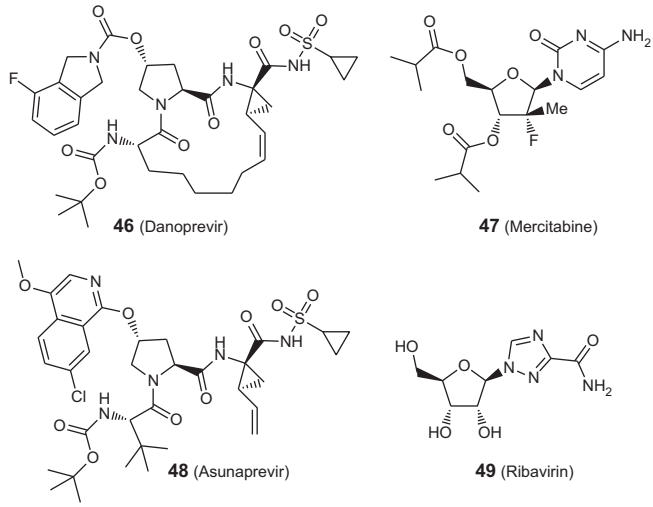

Figure 1.12 A subset of compounds investigated in seminal IFN-free HCV trials.

viral RNA that became undetectable upon retest 43 days later.[78,79] One G-1a subject had undetectable viral RNA at the end of treatment, but relapsed 4 weeks later. However, six of the G-1a-infected subjects experienced viral breakthrough, which occurred as early as week 3 and as late as week 12 of therapy, attributed to the selection of resistant variants which included Q30R, L31M/V and Y93C/N in the NS5A protein and R155K and D168A/E/T/V/Y in the NS3 protease domain. This study established for the first time that a chronic HCV infection could be cured without the use of interferon-α and/or ribavirin and is recognized as a watershed event in the therapy of the disease.[79]

Although the results suggest that more difficult to treat G-1a patients will require additional DAAs or the use of HCV inhibitors with a higher genetic barrier to resistance, the successful treatment of G-1b-infected subjects prompted a similar Phase 2a trial in a Japanese cohort with established null response to PEG-IFN/RBV.[80] In this study, daclatasvir (**1**) (60 mg qd) and asunaprevir (**48**) (initially 600 mg bid but subsequently reduced to 200 mg bid) were administered to 10 patients for 24 weeks, with nine subjects completing therapy and one patient discontinuing after 2 weeks. HCV RNA was undetectable in those who completed the course of therapy by 8 weeks and all nine achieved SVR_{12} and SVR_{24}, with no evidence of viral breakthrough during treatment or relapse post-treatment. Most interestingly, the patient who stopped therapy after 2 weeks and who had detectable HCV RNA (1.8 $\log_{10}$ IU mL^{-1}) at the time that therapy was discontinued, had undetectable levels of viremia measured on follow-up visits at weeks 2, 3, 4, 13 and 24 after discontinuation.[80]

GS-5885 is an HCV NS5A inhibitor for which early clinical data have been reported.[81] In a Phase 1 trial conducted in G-1-infected subjects, GS-5885 was