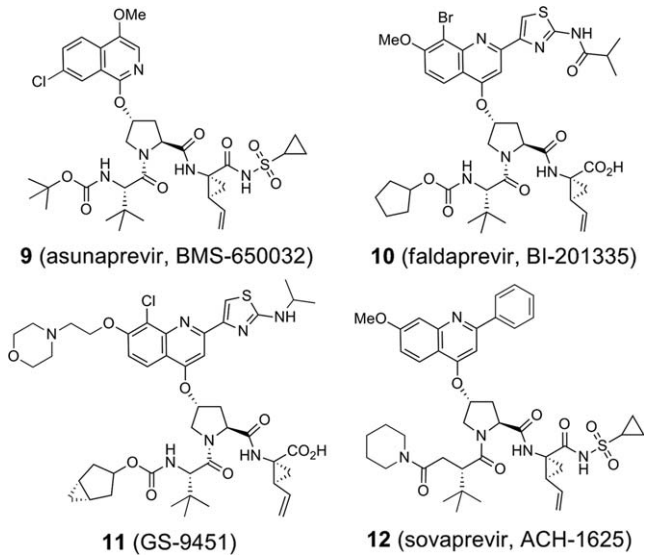

Figure 7.3 Acyclic HCV NS3 inhibitors.

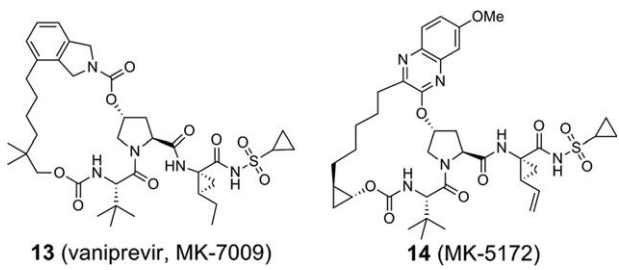

Figure 7.4 P1–P3 macrocyclic HCV NS3 inhibitors.

7.2 Discovery of Simeprevir (TMC-435350)

Following the clinical proof-of-concept established for the inhibition of the HCV NS3/4a protease mechanism of action with BILN-2061[22,51] (**4**, Figure 7.2), a number of research groups utilized this molecule as a starting point for novel compound/series development.

One such avenue of development that Medivir/Tibotec pursued was modification of the central *N*-acyl-(4*R*)-hydroxyproline core present in BILN-2061 and related acyclic analogs (**15**, Figure 7.5).[52] Replacement of proline with isosteric cyclopentane in inhibitors of other proteases has previously been demonstrated to be a successful strategy. Notably, Samuelsson and co-workers utilized dicarbonylcyclopentane **17** and -cyclopentene **18** to replace proline in a class of thrombin inhibitors[53,54] (Figure 7.6).