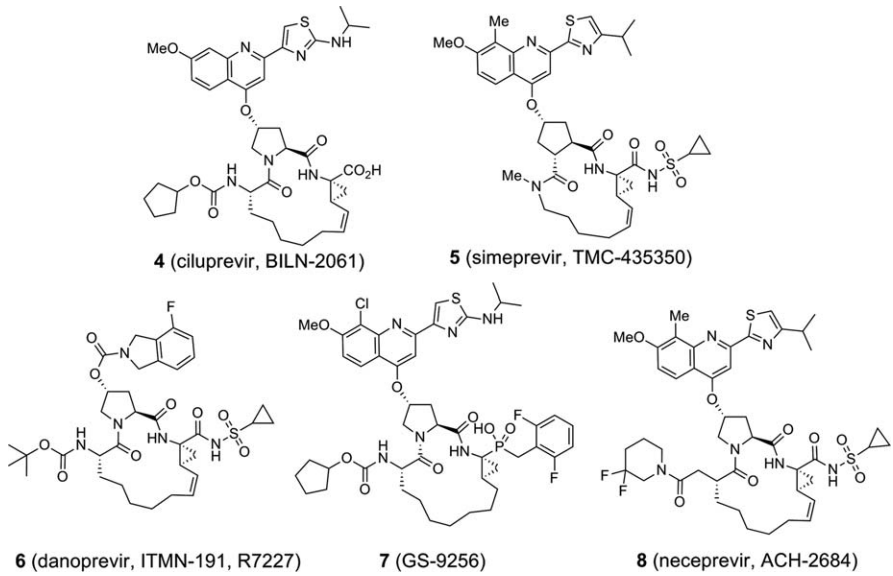

Figure 7.2 P1–P3 macrocyclic HCV NS3 inhibitors.

The reversible inhibitor structural class is significantly larger and can itself be broken down into three sub-classes based on structure: P1–P3 macrocyclic, acyclic and P2–P4 macrocyclic compounds.

The prototypical reversible inhibitor is a P1–P3 macrocyclic inhibitor, ciluprevir (BILN-2061),[22] **4**, (Figure 7.2) which demonstrated multi-log decreases in viral load during a Phase 1b study.[23] Development of BILN-2061 was subsequently discontinued due to cardiac findings in rhesus monkey safety studies.[24] Elaboration and modification of the P1–P3 scaffold core has provided multiple compounds that have advanced into clinical development. In addition to simeprevir (TMC-435350), **5**, which is discussed in more detail below, danoprevir (ITMN-191, R7227),[25–27] **6**, GS-9256,[28,29] **7**, and neceprevir (ACH-2684, **8**)[30] belong to this structural group.

The related acyclic chemical space has also yielded a number of clinical development candidates, including asunaprevir (BMS-650032),[31,32] **9**, faldeprevir (BI-201335),[33–37] **10**, GS-9451,[38,39] **11**, and sovaprevir (ACH-1625),[40] **12** (Figure 7.3).

The alternative P2–P4 macrocyclic constraint, derived from a modeling based approach,[41] led to vaniprevir (MK-7009),[42,43] **13**, and the second-generation inhibitor MK-5172,[44,45] **14**, described in detail below (Figure 7.4).

In addition, there are multiple HCV protease inhibitors in clinical development for which chemical structures have not been disclosed. These include ABT-450,[46] IDX-320[47,48] and PHX-1766.[49,50] In this chapter, we discuss in detail the design and discovery of three HCV NS3/4a protease inhibitors: simeprevir (TMC-435350, **5**), vaniprevir (MK-7009, **13**) and MK-5172 (**14**).