The modest genotype 1 SVR rates, coupled with significant adverse events (AEs), have stimulated a large effort to identify inhibitors of several key non-structural proteins essential for viral replication, with the NS3/4A HCV protease inhibitor area being the most well-populated and mature.[9]

Recent developments in the HCV protease area have significantly improved treatment options. Approval of the HCV NS3/4A protease inhibitors, boceprevir (Victrelis),[10,11] **1** (Figure 7.1), and telaprevir (Incivek/Incivo),[12,13] **2**, for treatment of HCV, in combination with pegylated IFN-α and ribavirin, represents a major step forward,[14] with enhanced SVR rates and the potential for shorter duration therapies.[15] In addition, patients who previously failed to achieve SVR with interferon/ribavirin alone can be retreated with these newly approved combinations and achieve significant SVR rates,[16] albeit lower than those observed in treatment-naive patients. These triple combinations now represent a new standard of care in HCV treatment.[17] However, a more dramatic paradigm shift in treatment of HCV infection appears all but certain in the coming years, with a move to all oral combination therapy with direct-acting antivirals (DAAs). HCV protease inhibitors have the potential to play a significant role in these DAA combination therapies, with the development of inhibitors of NS5A and NS5B also advancing. Clinical studies involving multiple permutations of nucleosides, ribavirin, NS3/4A protease and NS5A inhibitors are in progress across a range of patient populations and promising initial results have been obtained, including significant SVR rates.[18] While these studies will provide insight into both the number of drugs needed for combination therapy and the potential for even further shortened treatment duration, the individual profiles of the components in terms of cross genotype activity and resistance profile may make the drawing of general conclusions difficult.

HCV protease inhibitors can be classified by their modes of interaction with the protease, ketoamides that participate in slowly reversible covalent binding with the active site serine and more rapidly reversible inhibitors. Both of the first-generation HCV protease inhibitors, boceprevir and telaprevir, belong to the ketoamide class of molecules. Subsequent research in this area has been relatively limited, with narlaprevir (SCH 900518),[19] **3**, the only other compound disclosed that has moved into clinical development.[20,21]

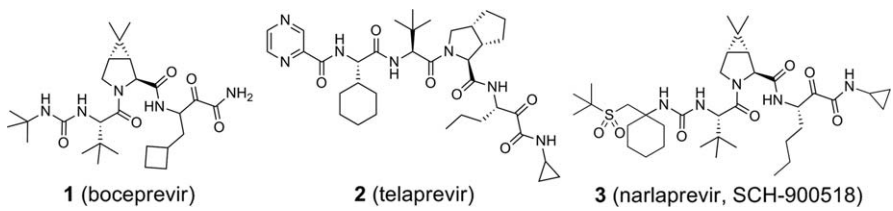


**Figure 7.1** Ketoamide HCV NS3 inhibitors.