Although the pyrrolidine moiety has been replaced by acyclic amines or by homologous heterocycles, the majority of the reported analogs incorporate functionalized pyrrolidines or five-membered heterocyclic variants in this region (Figure 1.10). Examples include the spirocyclic analog **38** and the bridged analog **39**, where the latter molecule also incorporates a number of the modifications described earlier and has featured prominently in a recent patent application disclosing combinations of advanced HCV therapeutic agents that encompass a range of alternate mechanisms.[49,50] In another example, a dimethylsilane moiety was incorporated into the 3-position of the pyrrolidine ring to afford **40**, claimed to be a potent G-1a/1b inhibitor.[51] Compound **41**, which is a peptidomimetic variant of **1**, exhibited potent G-1b inhibitory activity but is significantly weaker towards a G-1a replicon.[52]

Finally, additional distinct chemotypes with moderate levels of inhibitory activity in replicon systems and resistance mutations that map to HCV NS5A have been reported (see **42**–**44** in Figure 1.11).[53–56] Although some of the resistance mutations overlap with those observed for **1**, it is not apparent at this stage if they share a similar mode of inhibitory mechanism(s). It is noteworthy that a hybrid chemotype containing pharmacophore elements derived from **1** and **43** has been claimed to exhibit potent inhibitor activity towards both G-1a and G-1b replicons (see **45**).[57]

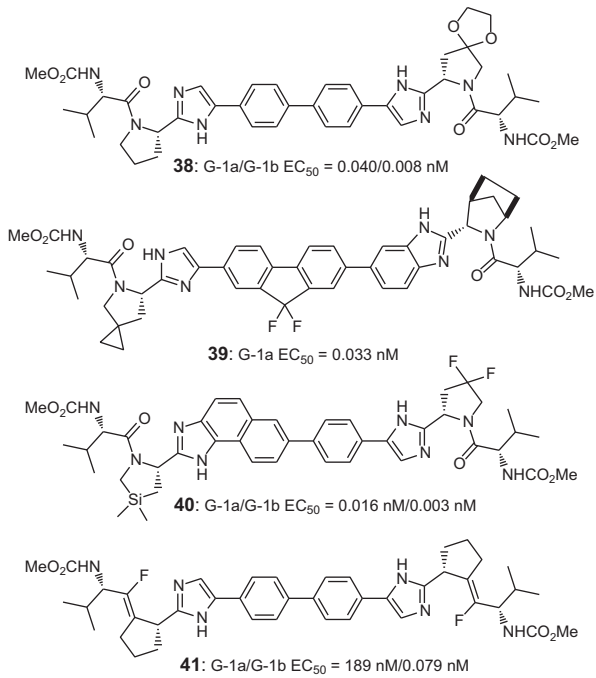

Figure 1.10 Analogs with peripheral modifications.