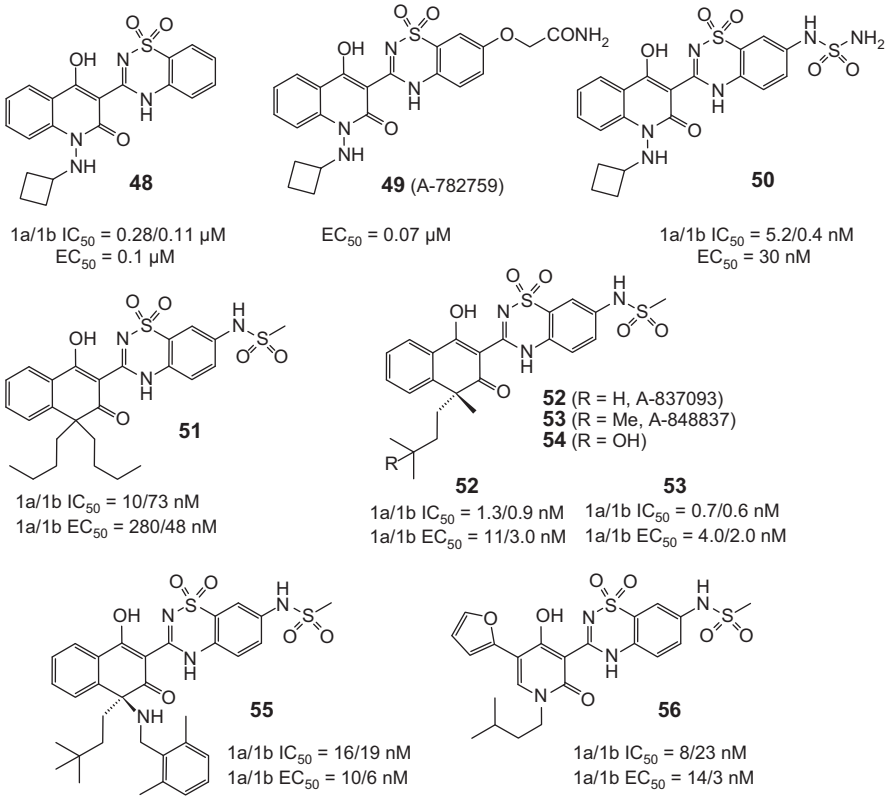

Figure 8.12 Benzothiadiazine palm site 1 inhibitors from Abbott Laboratories.

to be roughly equivalent in potency and the N1 methylene side-chain linker was shown to be replaceable by a nitrogen atom (*e.g.*, **48**, Figure 8.12). Interestingly, as biochemical potencies were being tracked using both gt1a and 1b enzymes, the 1a polymerase was often found to be more discriminating than the 1b enzyme and more sensitive to N1 structural modifications.[72a] Abbott also described C7-substituted analogs with improved profiles.[72b,c] For example, 7-alkoxyacetamide analog **49** (A-782759) displayed improved replicon potency and pharmacokinetic profiles compared with previously described analogs,[73a] while the corresponding sulfonamide or sulfamide (**50**) provided dramatically improved potency in this series ($EC_{50} = 3$ nM), remaining <100 nM when the replicon assay was performed in presence of 40% serum.[73b]

Whereas in replicon experiments A-782759 (**49**) and a protease inhibitor (BILN, 2061, celuprevir) alone were not able to reduce HCV RNA to undetectable levels due to the emergence of resistant mutants (M414T in the case of **49**), a combination of NS5B inhibitor **49** and celuprevir resulted in undetectable replicon RNA after 16 days, suggesting that such combinations could be effective at suppressing emergence of pre-existing resistant mutations in the