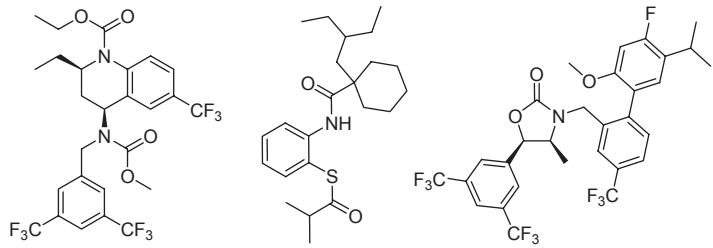
need is urgent. For example, while it is clear that Alzheimer's disease is pressing medical need,[41] to date there are no disease modifying therapies available, despite the extraordinary amount of capital expended in an effort to identify useful therapies. This is in part due to the lack of proven targets for Alzheimer's disease. Similarly, while there is a clear and pressing need for additional treatments for schizophrenia,[42] the current level of understanding of the disease state and lack of sufficient animal models[43] is a hindrance to progress in this important area.

There are also drug targets that have a theoretical connection to a particular disease state, but have as yet to be proven relevant to the human condition through the application of an appropriate chemotherapeutic agent. Cholesteryl ester transfer protein (CETP), for example, plays a key role in the interconversion of high density lipoproteins (HDL) and low density lipoproteins (LDL), and it has been suggested that inhibitors of this enzyme would have a positive impact on patients suffering from hypercholesterolemia.[44] While potent CETP inhibitors have been identified, such as Torcetrapib (CP-529,414)[45] and Dalcetrapib (JTT-705)[46] (Figure 1.9), none have



Torcetrapib (CP-529,414) | Dalcetrapib (JTT-705) | Anacetrapib (MK-0859)

FIGURE 1.9 Torcetrapib (CP-529,414), Dalcetrapib (JTT-705), and Anacetrapib (MK-0859) are cholesteryl ester transfer protein (CETP) inhibitors that have been clinically studied as potential treatments for hypercholesterolemia. Torcetrapib increased HDL levels and decreased LDL levels, but increased mortality rates, while Dalcetrapib was not efficacious in clinical trials. Anacetrapib increased HDL levels and decreased LDL levels, and did not negatively impact mortality rates.

been approved for marketing as the clinical candidates examined to date failed to demonstrate statistically significant beneficial effects in patients. It is possible that these results are an indication that CETP inhibition is not a viable drug target for the treatment of cardiovascular disease. It is also possible, however, that the clinical candidates examined to date are flawed in ways unrelated to the CETP that prevented them from functioning in the desired manner (e.g., off-target effects, pharmacokinetic issues).

In the case of Torcetrapib (CP-529,414), clinical trial data demonstrated that the drug candidate increased HDL levels and decreased LDL levels,