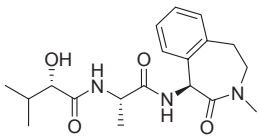
indicating that clinical efficacy could be achieved.[47] Unfortunately, the clinical candidate also caused increase in blood pressure and mortality rates, leading to the termination of clinical development in 2006.[48] Dalcetrapib (JTT-705) clinical studies were terminated by Roche in 2012 due to lack of efficacy.[49] On the other hand, clinical trials with Anacetrapib (MK-0859, Figure 1.9),[50] which also targets CETP, have successfully demonstrated that this compound can increase HDL levels and decrease LDL levels without increase in blood pressure or increased risk of cardiovascular disease-related deaths or events.[51] As of the writing of this text, the value of CETP as a drug target remains an unanswered question.

A similar scenario has surrounded γ-secretase inhibition. While it is known that γ-secretase plays a key role in the formation and deposition of amyloid plaques during the progression of Alzheimer's,[52] inhibitors of this key enzyme have failed to provide the clinically beneficial results expected. Semagacestat (LY450139, Figure 1.10), a compound developed




Semagacestat
(LY450139)

**FIGURE 1.10** The γ-secretase inhibitor Semagacestat (LY450139) failed to improve cognitive function in Alzheimer's patients, despite the fact that it lowered amyloid plaque formation.

by Eli Lilly inhibits γ-secretase, shows a dose-dependent lowering of amyloid plaque formation in humans, but did not improve cognitive function in patients. In fact, Semagacestat produced statistically significant declines in cognitive function compared to the placebo group in clinical trials.[53] Once again, this raises the question as to whether the target pathway is a dead end for treatment of the disease in question or if the compound in question is flawed in some unforeseen manner. In the case of Semagacestat (LY450139), it is possible that unexpected off-target activity may be clouding the clinical results. Semagacestat (LY450139) also interferes with Notch signaling, which plays a key role in cognitive function,[54] and it is not unreasonable to suggest that Notch signaling modulation masked potential positive effects that might have been observed if this off-target activity was absent.

The unanswered question raised by the failures of clinical candidates such as Torcetrapib (CP-529,414) and Semagacestat (LY450139) highlights the risks associated with choosing a target that is not clinically proven, as well as the potential for negative clinical results to be clouded by factors not related to the targeted mechanism. There are, however, substantial financial incentives to attempt to develop a "first-in-class" therapeutic agent. Prior to the introduction of the statins (or HMG-CoA reductase inhibitors),[55] there