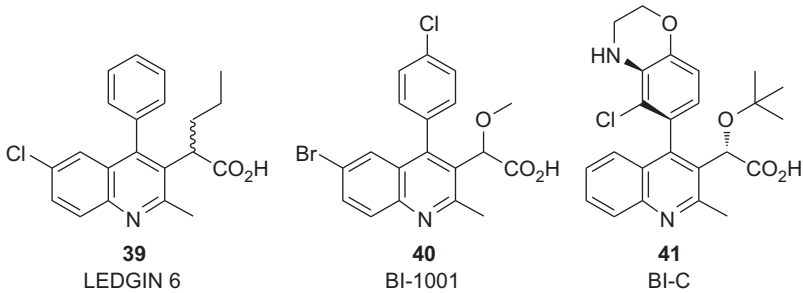

Figure 6.15 Structures of LEDGIN 6, BI-1001 and BI-C.

originally discovered as part of a high-throughput screen for integrase 3′ processing activity (see Figure 6.15, **41** for a representative example).[129] The lead compound, BI224436, has excellent ADME and antiviral properties and was advanced into Phase 1a clinical trials to evaluate safety and dosing in healthy volunteers. Using the PhenoSense assay to measure antiviral activity against 200 clinical isolates, BI224436 had a mean IC_{50} of 13 nM. As observed with the LEDGIN class of inhibitor, there was no decrease in potency against RAL-resistant viruses.[130] In a double-blind, placebo-controlled, single-rising dose escalation, BI224436 proved safe and well tolerated up to the highest dose group of 200 mg. Overall, BI224436 demonstrated a dose-proportional increase in plasma C_{max} and AUC and was rapidly absorbed with a median t_{max} of 0.5 h and a $t_{\frac{1}{2}}$ of 7.1 h. Based on the PK profile, an oral solution dose of 100 mg qd provided the target therapeutic plasma drug concentration of 500 nmol L^{-1} at 24 h.[131] For undisclosed reasons, the development of BI224436 was stopped following the initial phase 1 study. In late 2011, Boehringer Ingelheim entered a licensing agreement with Gilead Sciences to develop this series of NCINI further.

Although the understanding of the mechanism of action for these types of inhibitors will likely evolve over time, it is clear that these molecules inhibit the HIV-1 IN enzyme in a manner unique to the current INIs. Owing to the structural similarity between the LEDGIN and tBPQA class of NCINI, it is difficult to reconcile the reported differences in mechanism of action between these molecules. A recent study refuted the original claim that LEDGIN 6 was devoid of 3′ processing activity and reported it to be a low micromolar inhibitor of 3′ processing ($IC_{50} = 3.9\,\mu M$) similar in activity to BI-1001 ($IC_{50} = 2.3\,\mu M$; **40**, Figure 6.15).[132] Crystal structures for both **39** and **40** bound to the HIV-1 IN CCD reveal that the molecules occupy nearly identical spaces with the major difference being an additional H-bond interaction of the BI-1001 methoxy group with T174 of IN. Additionally, both classes of molecule promote integrase multimerization.[132] This alternative mechanism has been well documented to play an important role in viral replication as precise coordination of the multimeric state of IN is required to bind viral DNA productively.[126,133] The mechanistic details for inhibition are obviously complex, but a consensus appears to be forming around the concept of a