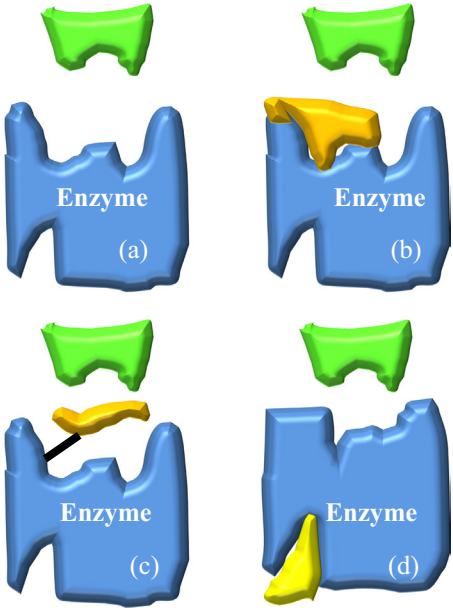

FIGURE 3.17 (a) In the normal enzyme process, substrates (green) interacts with active sites. (b) Competitive inhibitors (orange) reversibly blocks the active site. (c) Irreversible inhibitors (orange) covalently bind to the active site. (d) An allosteric inhibitor (yellow) binds to an allosteric binding site, altering the active site, preventing substrate binding.

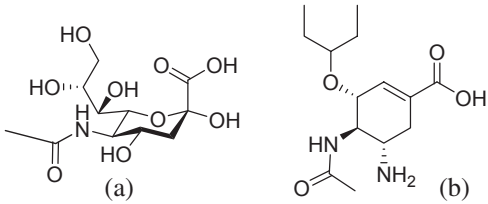

FIGURE 3.18 (a) Sialic Acid (b) GS-4071.

their substrates via an ATP-mediated process. With over 500 known examples, this class of enzymes has been the subject of intense study. They are critical to the majority of cellular functions, especially those related to signal transduction in both normal and disease states.[25] While the substrate for any particular kinase may be different, and therefore require different amino acid sequences for binding, ATP does not change its structure from one kinase to another. Nature has taken advantage of this by recycling the ATP-binding motif in the vast majority of kinase enzymes, leading to a significant level of homology within this family. While this may be efficient for nature, it can create a significant selectivity issue for competitive inhibitors of kinases that target the ATP-binding domain of the active site. In other words, kinases with very different phosphorylation substrates may have similar, perhaps identical ATP-binding domains, making the task of designing a compound that selectively inhibits one kinase over the others very challenging.