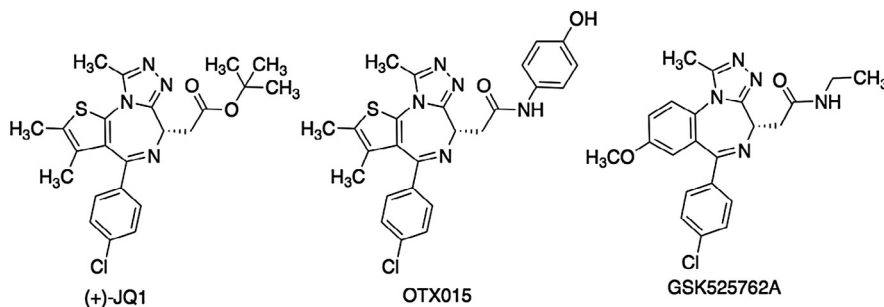


FIGURE 8.18

Prevention of Myc gene activation by the bromodomain blocker TEN-010

TEN-010 (NCT-01987362), whose structure has not been disclosed at the time of writing, is another highly selective, potent BET bromodomain inhibitor that occupies the bromodomains of BRD4 and prevents binding to the *Myc* gene. As a result, BRD4 no longer activates *Myc* gene expression, resulting in decreased proliferation and cancer cell death (Figure 8.18). It has entered phase I clinical trials in patients with NMC.



X-ray crystal structures of JQ1 and GSK525762A in complex with BRD4 showed nearly identical interactions, with the methyltriazole moiety occupying the acetyl lysine binding site of the protein (KAc). The two adjacent nitrogen atoms of the 1,2,4-triazole ring mimic the carboxy group of acetyl lysine and give a hydrogen bond with the  $\text{NH}_2$  group of asparagine 140 and a water-mediated hydrogen bond with the hydroxy group of tyrosine 97. The methyl substituent of the triazole binds to a small hydrophobic pocket—the same one that is occupied by the methyl fragment of the acetyl group in acetyl lysine (Figure 8.19).

Another potential application of bromodomain inhibitors is the treatment of heart disease because BET proteins regulate the growth of heart muscle cells and activate a broad set of genes involved in heart failure. Thus, treatment with JQ1 inhibited this abnormal pattern of gene activity and protected against heart wall thickening, the formation of scar tissue, and pump failure in a mouse model of cardiac disease. RVX208 is a bromodomain inhibitor that has been specifically designed for the treatment of cardiovascular disease and is in phase II clinical studies.