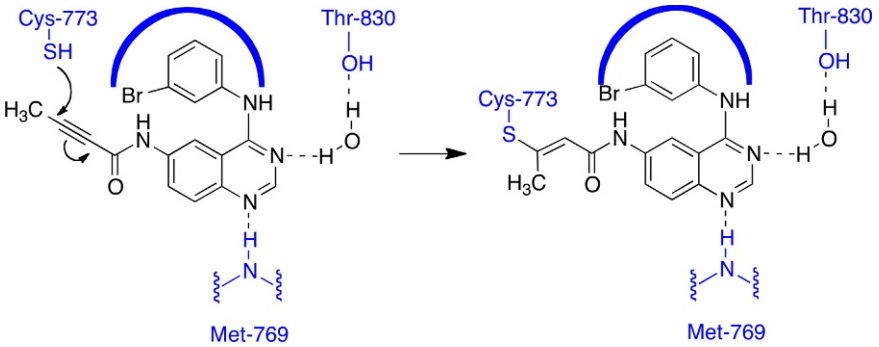
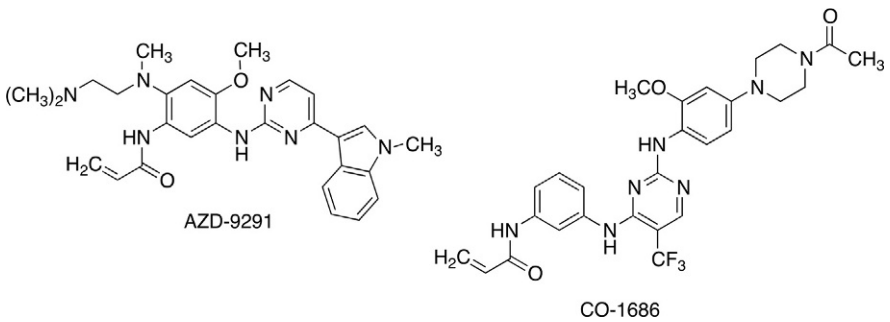


FIGURE 10.10

Binding of EKI-785, an irreversible EGFR inhibitor.

They include AZD-9291 and CO-1686, both of which are irreversible inhibitors of the T790M-mutated enzyme.[34] AZ-5104, a metabolite of AZD-9291, is also a potent inhibitor of mutated EGFR and may contribute to the efficacy of the latter.[35]



4.1.2 Monoclonal Antibodies Acting as Inhibitors of EGFR

Because antibodies recognize specific proteins with high specificity, they can be used as antagonists of the binding of an overexpressed protein to its ligands, although they are not devoid of toxic side effects (antibody-mediated cellular cytotoxicity). The role of monoclonal antibodies (mAbs) in cancer treatment is analyzed in Section 2 of Chapter 12, but some examples appear previously because they are discussed together with their specific targets.

Antibodies for EGFR prevent the binding of EGF or TGF-α, and hence receptor dimerization and signal transduction, in addition to causing receptor internalization and proteosomal degradation. Cetuximab (IMC-C225, Erbitux®) is a chimeric monoclonal antibody* approved in 2004 for EGFR-expressing metastatic colorectal carcinoma. This approval was later extended for other

*A chimeric protein is one that is encoded by a nucleotide sequence made by splicing together two or more complete or partial genes, which can even be from different species.