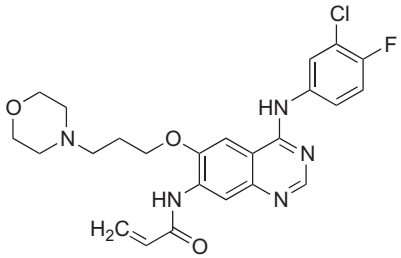
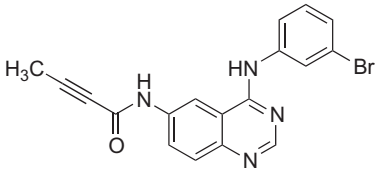
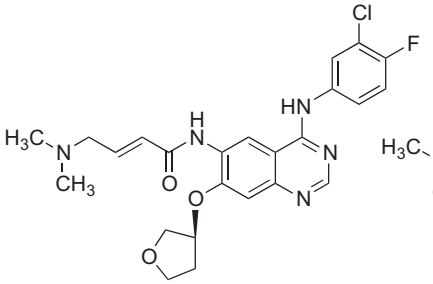
second-line therapy for NSCLC,[32] and it is also in clinical trials for breast, prostate, head, and neck cancer and glioma.



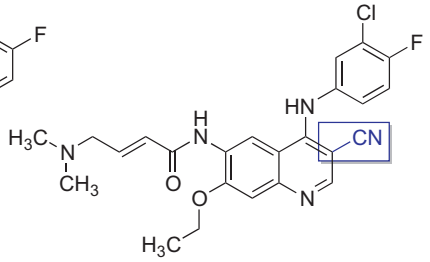
Canertinib (CI-1033)



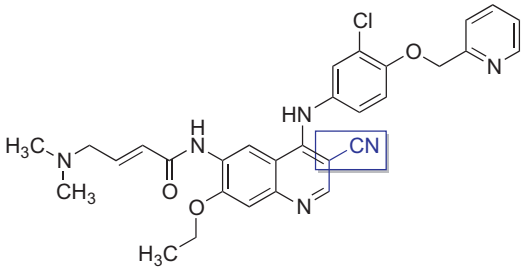
EKI-785



Afatinib (BIBW-2992))



Pelitinib (EKB-569)



Neratinib (HKI-272)

These compounds can be considered as active site-directed irreversible inhibitors because they contain a 4-anilinoquinazoline structural fragment (replaced in some of them by a 3-cyanoquinoline) that can be recognized by the ATP site and also an electrophilic α,β-unsaturated carbonyl moiety, responsible for covalent binding to the enzyme. The conserved cysteine residue Cys-773 within the ATP binding pocket seems to be responsible for the nucleophilic attack to these Michael substrates, as shown in Figure 10.10 for the case of EKI-785.[33]

Mutations of EGFR confer a drug-resistant state that does not diminish the kinase activity of the receptor but enhances its affinity for ATP while decreasing the affinity for the EGFR inhibitors. The most relevant mutation is T790M, which is present in 50–60% of patients who develop resistance to EGFR inhibitors (see Chapter 14, Section 9.2). Although there are currently no approved treatments for these patients, some investigational third-generation EGFR inhibitors have shown activity in them.