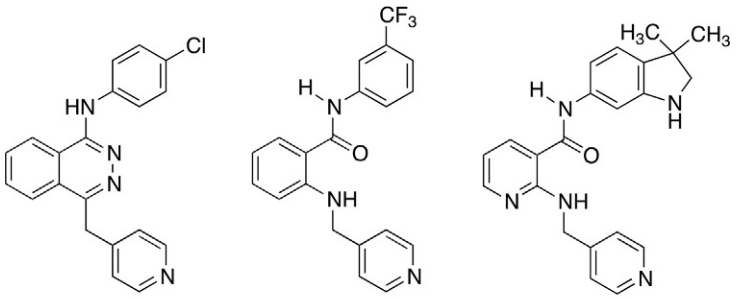

Vatalanib (PTK-787, ZK-222584) AAL-993 (ZK-260255) Motesanib (AMG 706)

The crystal structure of the drug–protein complex showed that, similarly to imatinib (see later), AAL-993 targets the inactive conformation of the enzyme. The binding involves three hydrogen bond interactions (Figure 10.13) and several hydrophobic interactions. The phenyl ring of the anthranilamide unit is sandwiched between the hydrophobic side chains of Val-916 and Lys-868, and the trifluoromethylphenyl substituent fits a lipophilic pocket.[63]

Quinazolines were initially developed as EGFR tyrosine kinase inhibitors and later refined to give VEGFR-2-selective compounds. Among other members of this family, vandetanib (ZD-6474, Zactima®, Caprelsa®) demonstrated therapeutic efficacy in a phase III trial of patients with advanced medullary thyroid cancer,[64] having been approved for this indication in 2011 by the FDA and in 2012 by the European Medicines Agency (EMA). Vandetanib occupies the ATP adenine binding site, where it forms a single hydrogen bond involving its N-1 nitrogen and the Cys-912 residue of the protein. Several structure–activity relationships (SARs) have been deduced for this family, including an increased activity for the 2-fluoro and 5-hydroxy derivatives, the latter effect being attributed to the formation of an additional hydrogen bond.[65] Another promising quinazoline derivative that acts on VEGFR signaling is cediranib (AZD-2171, Recentin®), which is undergoing a number of clinical trials (phase I and phases II/III) to evaluate its potential role in the treatment of a range of solid tumors.[66] Recent clinical trials have shown that its combination with the PARP inhibitor olaparib is significantly active in recurrent platinum-sensitive ovarian cancer.

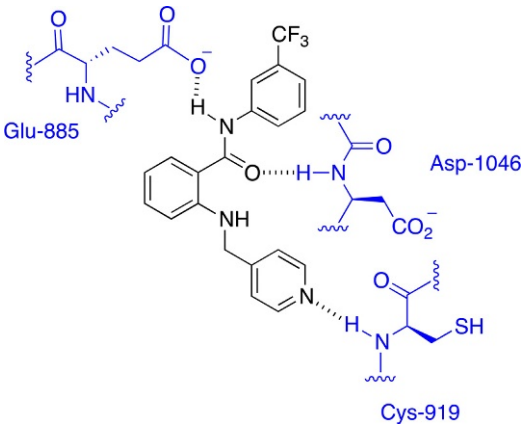

FIGURE 10.13

Binding of AAL-993 to VEGFR-2.